

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

Technology Center: 1600

Adams, et al.

Attorney Docket No. 21477 US

Application No.: 10/700,417

Art Unit: 1626

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Examiner: Laura Stockton

FOR: NOVEL SUBSTITUTED OXAZOLE DERIVATIVES

APPEAL BRIEF

Nutley, New Jersey 07110 February 16, 2006

Mail Stop: Appeal Brief - Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal which was filed on November 16, 2005, Applicants submit this Appeal Brief appealing the final Office Action dated August 17, 2005, rejecting claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52 and 53 and objecting to claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49. Submitted herewith (in duplicate) is: (1) the appropriate document authorizing payment of the required fee in connection with the filing of this Appeal Brief under 37 C.F.R. § 41.20(b)(2); and (2) a Petition for Extension of Time for one month accompanied by the appropriate provision authorizing payment of the required fee.

I. REAL PARTY IN INTEREST

The rights to this application have been assigned to Hoffmann-La Roche Inc. which is a subsidiary of Roche Holding AG (the real parties of interest).

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 51 and 54-56 were withdrawn by the Examiner as nonelected. Claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52 and 53 were rejected by the Examiner and claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49 were objected to by the Examiner as being dependent upon a rejected base claim but would otherwise be allowable by the Examiner if rewritten in independent form. A copy of appealed claims 1-50, 52 and 53 is attached hereto in the Claims Appendix.

The appealed grounds for rejection apply to all of the <u>rejected</u> claims. As noted, however, claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49 were only <u>objected to</u> as depending from one or more rejected claims. Since the claims that were only objected to have been indicated to be allowable if rewritten in independent form they do not stand or fall on the same grounds of rejection as the rejected claims.

IV. STATUS OF AMENDMENTS

No amendments were filed after the final Office Action of August 17, 2005 rejecting claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52 and 53 and objecting to claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

This claimed subject matter is directed to compounds encompassed by formula (I):

$$R^{1} \xrightarrow{O} R^{2} R^{3} \qquad R^{4} \xrightarrow{O} R^{7} \qquad (I)$$

wherein:

R¹ is alkyl, fluoro-lower-alkyl, cycloalkyl, bicyclic cycloalkyl, or tricyclic cycloalkyl;

R² is hydrogen, lower-alkyl, or fluoro-lower-alkyl;

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower-alkyl, fluoro-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy, fluoro-lower-alkoxy, hydroxy-lower-alkoxy, lower-alkoxy, lower-alkoxy, and lower-alkenyl, wherein at least one of R³, R⁴, R⁵, or R⁶ is not hydrogen, or

 R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are -CH=CH-S-,

-S-CH=CH-, -CH=CH-O-, -O-CH=CH-, -CH=CH-CH=CH-, -O-(CH₂)₂₋₃-, -(CH₂)₂₋₃-O-, or -(CH₂)₃₋₅-, and
$$R^5$$
 and R^6 are as defined above,

R⁷ is lower-alkyl, fluoro-lower-alkyl, lower-alkenyl, aryl, or aryl-lower-alkyl;

R⁸ is hydrogen or lower-alkyl;

n is 1, 2 or 3;

or pharmaceutically acceptable salts or pharmaceutically acceptable esters thereof.

Support for the claimed subject matter can be found throughout the specification, particularly at page 6, paragraph [0025] to page 13, paragraph [0033].

VI. GROUNDS OF REJECTION

Claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52, and 53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 91/19702 ("Hulin"), taken alone or in combination with the teachings of WO 02/16331 ("Brooks"). According to the Examiner, the claimed compounds would have been obvious to one skilled in the art.

Claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49 are objected to by the Examiner as being dependent upon a rejected base claim (above) but would otherwise be allowable if rewritten in independent form.

A copy of the final Office Action dated August 17, 2005, as well as copies of the references cited by the Examiner in the Office Action are attached hereto in the Evidence Appendix.

VII. ARGUMENT

1. Obviousness Rejection Under 35 U.S.C. § 103(a)

A. Claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52, and 53

(1) The Examiner's Rejection

According to the Examiner, Hulin teaches oxazole compounds that are structurally similar to the claimed compounds. The Examiner cites example 13 on page 39 of Hulin and pages 6-7 of Hulin disclosing formula II wherein the Examiner selected alkyl as a species of Z, alkyl as a species of Z¹, O as a species of X, N as a species of Y, 2 as a species of m, O as a species of W, no bond as a species of the "-----" symbol, O as a species of X¹, alkyl as a species of R, and hydroxyl as a species of Y¹. According to the Examiner, the resulting oxazole compound is structurally similar to a compound falling within the genus of the Applicants claimed invention, differing only by a hydrogen substituent versus an alkyl substituent (for which Brooks teaches the interchangeability of hydrogen and alkyl). According to the Examiner Brooks teaches the interchangeability of hydrogen versus an alkyl group on the phenyl ring of formula II in Hulin.

(2) Summary of Applicants' Arguments In Response

Claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52, and 53 are not obvious because: (1) there is no structural similarity between any compound disclosed in Hulin or Brooks and the claimed invention for the reasons stated below; (2) there is a lack of motivation to combine Hulin with Brooks for the reasons stated below; and (3) even if there was motivation to combine Hulin with Brooks and even if the compound identified by the Examiner in Hulin or Brooks could be considered structurally similar to a compound encompassed by the genus of the claimed invention, there is no motivation to select such a structurally similar compound and then modify it to arrive at the claimed invention.

(3) The Law of Obviousness Under 35 U.S.C. § 103

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the <u>differences</u> between the subject matter sought to be patented and the prior art are such that the subject matter <u>as a whole</u> would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (emphasis added). 35 U.S.C. § 103(a).

Under 35 U.S.C. § 103, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Graham v. John Deere*, 383 U.S. 1, 148 U.S.P.Q. 459, 467 (1966) (emphasis added). The following tenets of patent law must be considered and adhered to when applying 35 U.S.C. § 103:

- (A) The claimed invention must be considered as a whole;
- (B) The references must be considered <u>as a whole</u> and <u>must suggest the desirability</u> and thus the obviousness of making the combination; and
- (C) The references must be viewed <u>without the benefit of impermissible hindsight</u> vision afforded by the claimed invention.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986).

For claims directed to chemical compounds, "obviousness requires 'structural similarity between claimed and prior art subject matter . . . [but only] where the prior art gives reason or motivation to make the claimed compositions." Yamanouchi Pharmaceutical Co., Ltd. et al. v. Danbury Pharmacal, Inc. et al., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (emphasis added); In re Mills, 916 F.2d 680, 682 (Fed. Cir. 1990) (the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination); Al-Site Corp. v. VSI Int'l Inc., 174 F3d 1308, 1323-24 (Fed. Cir. 1999) (obviousness requires some motivation or suggestion to modify or combine the prior art

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teachings but the fact that a claimed invention was within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish obviousness).

In addition, "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." In re Baird 16 F.3d 380, 382 (Fed. Cir. 1994) ("While the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables.") (emphasis added). "[H]omology should not be automatically equated with prima facie obviousness." In re Langer, 59 C.C.P.A. 1256, 1260, 465 F.2d 896, 899 (CCPA 1972) (Claims to a polymerization process using a sterically hindered amine were held unobvious over a similar prior art process because the prior art disclosed a large number of unhindered amines and only one sterically hindered amine (which differed from a claimed amine by 3 carbon atoms), and therefore the reference as a whole did not apprise the ordinary artisan of the significance of hindered amines as a class). See also In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992) (reversing obviousness rejection of novel dicamba salt with acyclic structure over broad prior art genus encompassing claimed salt, where disclosed examples of genus were dissimilar in structure, lacking an ether linkage or being cyclic); and Ex parte Burtner and Brown, 121 U.S.P.Q. 345, 347 (Bd. of App. 1951) (holding claimed alcohols patentable over prior art compounds differing by a -CH2- group). Copies of the above-referenced cases are attached hereto in the Case Appendix. In the *In re Langer* case, the court held that:

We view appellants' invention "as a whole" as being the use of sterically hindered amines as opposed to unhindered amines in a known process to solve a particular problem We do not think the [prior art] patent provides a basis for the use of sterically hindered amines as a class, or of any of the amines encompassed by appellants' claims ... The presence in the reference of an isolated hindered amine ... does not, by itself, apprise the ordinary artisan of the significance of hindered amines as a class when "all of the disclosures in a reference" are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference. In re Langer, 465 F.2d at 899 (emphasis added).

Similarly, the court in the *In re Baird* case held that while a prior art genus unquestionably encompasses the claimed invention when certain variables are chosen, there is

nothing in the disclosure of the prior art reference to suggest that one should select such variables:

While the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables.

* * * *

Given the <u>vast number</u> of diphenols encompassed by the generic diphenol formula in Knapp and the fact that the diphenols that Knapp specifically discloses to be 'typical,' 'preferred,' and 'optimum,' <u>are different from and more complex</u> than bisphenol A, <u>we conclude that Knapp does not teach or fairly suggest the selection of bisphenol A. *In* re Baird 16 F.3d at 383 (emphasis added)</u>

(4) The Claims Are Not Obvious

Here, in the present application, the Examiner is making an obviousness rejection on the same basis as the Examiners in the *Baird* and *Langer* applications made which was held to be improper and was reversed by the U.S. Court of Appeals, Federal Circuit and the U.S. Court of Customs and Patent Appeals, respectively. Like the *In re Baird* and *In re Langer* cases, the prior art reference discloses only an isolated possibility of a compound (from a broad genus) that the Examiner argues is structurally similar to the compounds of the claimed invention.

In attempting to show obviousness, the Examiner (using impermissible hindsight) had to actively seek out and select formula II (from formulas I and II in Hulin) and then had to actively seek out and select various substituents from formula II to arrive at an oxazole compound that the Examiner argues is structurally similar to an oxazole compound covered by the Applicants' claimed invention. *See* pages 6-7 of Hulin in the Evidence Appendix showing formulas I & II of Hulin compared to the Applicants' claimed invention as shown in the Claims Appendix. In addition, the Examiner can only identify a single example (example 13, on page 39 of Hulin) out of 26 examples disclosed in Hulin that the Examiner argues is structurally similar to the claimed invention (2-Methoxy-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]phenyl]propanoic acid). Moreover, this example (example 13, on page 39 of Hulin) is not even a homolog, isomer, or otherwise structurally similar to any of the compounds in any of the Applicant's claims. This is

because, Example 13 on page 39 of Hulin requires an aromatic phenyl group (A) in the 2 position on the oxazole:

In contrast, the R¹ group in the 2 position on the oxazole of the claimed invention cannot be an aromatic phenyl (but rather must be an alkyl, fluoro-lower-alkyl, cycloalkyl, bicyclic cycloalkyl, or tricyclic cycloalkyl). *See* claim 1 and the definition of alkyl, cycloalkyl, bicyclic cycloalkyl, etc. on pages 3-5 of the Applicants' specification. Furthermore, more then 95% of the compounds falling under the two generic formulas in Hulin are not even oxazoles (in contrast to the Applicants' claimed invention which is entitled, "Novel Substituted Oxazole Derivatives).

Brooks discloses a very broad genus of oxazoles (formula I), several subgenera and over 140 examples of species. The Examiner cites the generic formulas on pages 4-6 of Brooks and identifies only a single example (example 14, page 83 of Brooks) that she argues is structurally similar to the compounds covered by the claimed invention. However, all the generic formulations and species disclosed in Brooks (including the single example cited by the Examiner), are not homologs, isomers, or otherwise structurally similar to the claimed invention since all the compounds in Brooks require an alkyl or haloalkyl at the R³ position as shown in formula I of Brooks. In contrast, all of the compounds of the Applicants' claimed invention lack this R³ substituent.

Furthermore, the Applicants' claimed compounds always require an alkoxy group $[(CH_2)_n-O]$. In contrast, only one fourth of the compounds encompassed by formula I in Brooks has this alkoxy group since the W in formula I of Brooks is selected from the group consisting of CH_2 , CH(OH), C(O) and O. In addition, the Applicants' claimed compounds have a central phenyl moiety. In contrast, only one half of the compounds encompassed by formula I in Brooks has this central phenyl moiety since the Y in formula I of Brooks is an unsubstituted or

substituted thiophen-2,5-diyl or phenylene. Furthermore, many of the choices for the other substituents in the generic formulations disclosed in Brooks are different than the corresponding substituents of the Applicants' claimed compounds.

Like the *In re Baird* case, there is no suggestion or motivation to select a compound close in structure to the claimed invention (or to otherwise to seek out and select a particular genus and various substituents within that genus to arrive at an oxazole compound that is structurally similar to the claimed invention) and to further modify such a compound to arrive at the claimed invention. As in the *In re Langer* case, both Hulin and Brooks fail to "apprise the ordinary artisan of the significance of the [Applicants' compounds] as a class." *In re Langer*, 465 F.2d at 899. In addition, there is no structural similarity between any compound disclosed in Hulin or Brooks and any compound claimed by the Applicants.

(a) The Scope And Content Of The Prior Art & The Difference Between The Prior Art And The Claims At Issue

Hulin discloses 3-aryl-2-hydroxypropionic acid derivatives and analogs as hypoglycemic agents and is directed to the compounds of two generic formulas (formula I and formula II). Formula I, including all of the numerous species disclosed in Hulin encompassed by Formula I, are completely different and unrelated to the Applicants claimed invention. For example, more than 90% (11/12) of the compounds encompassed by Formula I encompass non-oxazole compounds (in contrast to the oxazole compounds of Applicants' claimed invention) since in Formula I of Hulin, Y can be either CH or N, and X can be either S, O, NR2, -CH=CH-, -CH=N, or -N=CH. Moreover, regardless of whether the compounds encompassed by Formula I are oxazoles or not, group A in Formula I of Hulin is selected from various aromatic bicyclic rings in contrast to the corresponding -(CH2)n-O group of the claimed compounds. Thus, Formula I and all of the species encompassed by Formula I in Hulin are completely different and unrelated to the Applicants claimed invention.

Similarly, with respect to Formula II, more than 90% $\binom{11}{12}$ of the compounds encompassed by Formula II of Hulin encompass non-oxazole compounds (in contrast to the

oxazole compounds of Applicants' claimed invention) since again, Y can be either CH or N, and X can be either S, O, NR2, -CH=CH-, -CH=N, or -N=CH. Using impermissible hindsight, the Examiner had to actively seek out and select oxazoles from formula II and then had to actively seek out and select various substituents from formula II to arrive at a compound that the Examiner argues is structurally similar to a compound covered by the Applicants' claimed invention.

In addition, when viewing Formulas I & II together (when viewing Hulin as a whole) more than 95% of the compounds encompassed by the generic formulations of Hulin (Formulas I & II) encompass non-oxazole compounds (in contrast to the oxazole compounds of the Applicants' claimed invention). Viewing the small percentage of oxazole compounds encompassed by the generic formulations of Hulin, the Examiner identifies only one isolated possibility that the Examiner argues is structurally similar to a compound covered by the claimed invention (by again using impermissible hindsight derived from the Applicants' invention to actively pick and choose an oxazole from Formula II in Hulin from 11 other possible ring structures and then to actively pick and choose various substituents from a vast number of other possible substituents). Moreover, this isolated possibility from generic Formula II in Hulin that the Examiner argues is structurally similar to a compound covered by the claimed invention is not in fact structurally similar. This is because the central phenyl moiety in Formula II of Hulin must always be unsubstituted with hydrogen. In contrast, the central phenyl moiety of the claimed invention must always be substituted. See the central phenyl moiety in Formula II of Hulin on page 6 of Hulin in the Evidence Appendix and claim 1 of Applicants' invention in the Claims Appendix, wherein in claim 1 at least one of R³, R⁴, R⁵, and R⁶ is not hydrogen and must be selected from hydroxyl, halogen, lower-alkyl, fluoro-lower-alkyl, etc. or otherwise R^3 and R^4 must form a ring.

Moreover, the Examiner can only identify a single example of a specifically disclosed species (example 13, on page 39 of Hulin) out of 26 specifically disclosed species disclosed in Hulin that the Examiner argues is structurally similar to the claimed invention. Example 13, on

page 39 of Hulin discloses 2-Methoxy-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]phenyl]propanoic acid:

As shown in the above structure, this compound has an aromatic phenyl group (A) at the 2-position on the oxazole. In contrast, the R¹ group in the 2-position on the oxazole of the claimed invention can never be an aromatic phenyl (but rather must be an alkyl, fluoro-lower-alkyl, cycloalkyl, bicyclic cycloalkyl, or tricyclic cycloalkyl). *See* claim 1 and the definition of alkyl, cycloalkyl, bicyclic cycloalkyl, etc. on pages 3-5 of the Applicants' specification. Thus, example 13, on page 39 of Hulin (the only species out of 26 specifically disclosed examples in Hulin that the Examiner identifies and asserts to be structurally similar) is not structurally similar as the Examiner asserts. In fact, all of the specifically disclosed species in the examples of Hulin that are directed to oxazoles require an aromatic phenyl group at the 2-position on the oxazole (in contrast to the Applicants' claimed invention) and therefore are not structurally similar.

In addition, the range of possible species or choices for R, X, X^1 , Y, Y^1 , Z, Z^1 , and W in formula II of Hulin are much different and/or are extremely broad compared to the corresponding choices or species encompassed by formula I of the claimed invention. *See* the range of possible species or choices for R, X, X^1 , Y, Y^1 , Z, Z^1 , and W in formula II of Hulin on pages 6-7 of Hulin in the Evidence Appendix compared to the corresponding species or choices encompassed by formula I of the claimed invention as shown in claim 1 in the Claims Appendix. For example, the X in the five membered ring of Hulin can be S, O, NR^2 , -CH=CH-, -CH=N-, or -N=CH- and the Y in the five membered ring of Hulin can be N or CH in contrast to the single O (for the X) and the single N (for the Y) in the oxazole ring of the present invention. Similarly, the Z genus in Hulin can be hydrogen, amino, (C_1-C_7) alkyl, (C_3-C_7) cycloalkyl, phenyl, or phenyl mono- or disubstituted with (C_1-C_3) alkyl, trifluoromethyl, (C_1-C_3) alkoxy, phenyl, phenoxy, benzyl,

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benzyloxy, fluoro or chloro. In contrast, the corresponding R¹ genus of the presently claimed invention is limited to alkyl, fluoro-lower-alkyl, cycloalkyl, bicyclic cycloalkyl, or tricyclic cycloalkyl.

In addition, the Y^1 genus in Hulin can be hydroxyl, (C_1-C_3) alkoxy, phenoxy, benzyloxy, amino, (C_1-C_4) alkanoylamino, (C_1-C_4) alkanesulfonylamino, benzenesulfonylamino, napthalenesulfonylamino, di[(C_1-C_3) alkyl]aminosulfonylamino, or one of said groups mono- or disubstituted with (C_1-C_3) alkyl, trifluoromethyl, hydroxyl, (C_1-C_3) alkoxy, fluoro or chloro. In contrast, the group corresponding to Y^1 in the presently claimed invention is limited to COO-R⁸ wherein R⁸ is either hydrogen or lower-alkyl.

Moreover, the substitution pattern of the five membered cyclic ring in formula II of Hulin is extremely broad encompassing all substitution patterns for the attachment of Z and Z^1 to the ring and for the attachment of the ring to the compound. In contrast, the substitution pattern of the oxazole ring of the present invention is very specific in that R^1 is attached to the carbon between the N and O, R^2 is attached to the carbon adjacent to the O, and the ring itself is attached to the compound via the carbon on the ring adjacent to the N. Again, see claim 1 in the Claims Appendix compared to Hulin's Formula II on page 6 of Hulin.

Brooks discloses a very broad genus of oxazoles (formula I), several subgenera and over 140 examples of species. The Examiner cites the generic formulas on pages 4-6 of Brooks and identifies only a single example (example 14, page 83 of Brooks) that she argues is structurally similar to the compounds covered by the claimed invention. However, as stated above, all the generic formulations and species disclosed in Brooks (including the single example cited by the Examiner), are not homologs, isomers, or otherwise structurally similar to the claimed invention since all the compounds in Brooks require an alkyl or haloalkyl at the R³ position as shown in formula I of Brooks. In contrast, all of the compounds of the Applicants' claimed invention lack this R³ substituent. Moreover, the Applicants' claimed compounds always require an alkoxy group [(CH₂)_n-O]. In contrast, only one fourth of the compounds encompassed by formula I in Brooks has this alkoxy group since the W in formula I of Brooks is selected from the group

consisting of CH₂, CH(OH), C(O) and O. In addition, the Applicants' claimed compounds have a central phenyl moiety. In contrast, only one half of the compounds encompassed by formula I in Brooks has this central phenyl moiety since the Y in formula I of Brooks is an unsubstituted or substituted thiophen-2,5-diyl or phenylene.

Furthermore, many of the choices for the other substituents in the generic formulations disclosed in Brooks are different than the corresponding substituents of the Applicants' claimed compounds. For example, the R⁴ substituent in Formula I of Brooks is different than the corresponding R⁷ substituent of the Applicants' generic formula. The R⁴ substituent in Brooks is selected from the group consisting of a substituted or unsubstituted phenyl, napthyl, 1,2,3,4-tetrahydronapthyl, quinolyl, pyridyl and benzo[1,3]dioxl-5-yl. In contrast, the R⁷ substituent in the Applicants' claimed invention is selected from the group consisting of lower-alkyl, fluorolower-alkyl, lower alkenyl, aryl, and aryl-lower-alkyl.

(b) The Reference And The Claimed Invention Must Be Viewed As A Whole

The Examiner asserts that the differences enumerated above between the claimed invention and Hulin and Brooks is irrelevant. *See* the final Office Action on pages 7-13. For example, on page 9 of the final Office Action, the Examiner states that, "[i]n response [to Applicants' arguments], Formula I in Hulin was not relied upon in making the rejection of the instant claims under 35 U.S.C. 103," thus expressly admitting that Hulin was not viewed as a whole.

However, the Courts have ruled that prior art references must be considered <u>as a whole</u> and <u>must suggest the desirability</u> and thus the obviousness of making the combination. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986). In addition, the prior art references must be viewed <u>without the benefit of impermissible hindsight</u> vision afforded by the claimed invention. *Id.*

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Here, the Examiner does not consider Hulin and Brooks as a whole. When Hulin is viewed as a whole, it is evident that the Examiner has used impermissible hindsight and simply created or picked out a compound from the genus of Hulin's Formula II and a single example out of 26 examples disclosed in Hulin (example 13, on page 39 of Hulin [which is not even structurally similar for the reasons stated above]) to arrive at a compound that the Examiner argues is structurally similar to a compound covered by the claimed invention. Similarly, when Brooks is viewed as a whole, Brooks discloses a very broad genus (formula I) and over 140 examples of species which are not structurally similar for the reasons stated above. It is clear that the Examiner is using impermissible hindsight vision afforded by the claimed invention to seek out and select various substituents in an attempt to create a compound from a broad genus that she argues is structurally similar to a compound covered by the Applicants claimed invention.

When viewed as a whole, all the other compounds disclosed in Hulin (which were not cited by the Examiner) are not structurally similar to any compound covered by the claimed invention. Accordingly, as in the *In re Baird* and *In re Langer* cases, there is no motivation to select a compound close in structure to the claimed invention and then modify it to arrive at the claimed invention.

(c) There Is No Motivation To A Person Of Ordinary Skill In The Art

According to the Examiner, "the motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity." See the Office Action at page 5. Elsewhere, the Examiner states that "the motivation to prepare additional compounds embraced by Hulin lies in the fact that both Hulin and Brooks prepare specie which differ from the instant claimed compounds at only one or two positions." See the Office Action at p. 10.

However, this argument is unfounded for two reasons: (1) no structural similarity exists between any compound disclosed in Hulin or Brooks and any compound claimed by the Applicants for the reasons stated above; and (2) even if the compounds identified by the

Examiner in Hulin or Brooks could be considered structurally similar, no motivation exists to select such compounds and then modify them to arrive at the claimed. Again, see In re Baird 16 F.3d 380, 383 (Fed. Cir. 1994) (while a prior art genus unquestionably encompasses the claimed invention when certain variables are chosen, there is nothing in the disclosure of the prior art reference to suggest that one should select such variables. "Given the vast number of diphenols encompassed by the generic diphenol formula in Knapp . . . we conclude that Knapp does not teach or fairly suggest the selection of bisphenol A."); In re Langer, 59 C.C.P.A. 1256, 1260, 465 F.2d 896, 899 (CCPA 1972) (claims to a polymerization process using a sterically hindered amine were held unobvious over a similar prior art process because the prior art disclosed a large number of unhindered amines and only one sterically hindered amine (which differed from a claimed amine by 3 carbon atoms), and therefore the reference as a whole did not apprise the ordinary artisan of the significance of hindered amines as a class); In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992) (reversing obviousness rejection of novel dicamba salt with acyclic structure over broad prior art genus encompassing claimed salt, where disclosed examples of genus were dissimilar in structure, lacking an ether linkage or being cyclic); and Ex parte Burtner and Brown, 121 U.S.P.Q. 345, 347 (Bd. of App. 1951) (holding claimed alcohols patentable over prior art compounds differing by a -CH2- group).

In addition to the lack of motivation to select a compound close in structure to the claimed invention and then modify it to arrive at the claimed invention, there is a further lack of motivation to combine Hulin with Brooks. Viewing Hulin and Brooks as a whole, the compounds disclosed in Hulin and Brooks are (overall) different from each other. Hulin is entitled, "3-Aryl-2-Hydroxypropionic Acid Derivatives And Analogs As Hypoglycemic Agents." In contrast, Brooks is entitled, "Oxazoylyl-Arylpropionic Acid Derivatives And Their Uses As PPAR Agonists." Brooks primary focus is the use of its compounds as PPAR agonists and lists a number of diseases associated with the PPAR receptor including diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as, inflammatory bowel disease. Brooks at p. 3. According to Brooks, "the present invention relates to a method of modulating a peroxisome proliferator activated receptor [PPAR] by contacting the receptor with at least one compound of Structural Formula I . . ." Brooks at p. 4. Although Hulin teaches that

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its compounds may be used as hypoglycemic and hypocholesterolemic agents, it does not otherwise teach that its compounds bind to or activate PPAR receptors. In fact PPAR receptors are not even mentioned in Hulin. Thus, when each reference is viewed as a whole it is difficult to see why one skilled in the art would be motivated to combine Hulin with the teachings of Brooks since the compounds disclosed in each reference are (overall) different from each other and since Brooks is largely focused on PPAR activity while Hulin is more specifically focused on the treatment of hyperglycemia and hypercholesterolemia rather than the activation of the PPAR receptor.

In one section of the Office Action the Examiner appears to be relying on the capabilities of one of ordinary skill in the art to establish motivation. Indeed, on pages 11-12 of the Office Action, the Examiner states:

Applicants argue that there is no motivation to combine the teachings of Hulin and Brooks et al. This argument is not persuasive. The test for combining references is not what individual references themselves suggest but rather what the combination of disclosures taken as whole <u>would suggest to one of ordinary skill in the art</u> (emphasis added).

However, as stated above, the Federal Circuit has held that the level of skill in the art cannot be relied upon to provide the suggestion to modify or combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F3d 1308, 1324 (Fed. Cir. 1999) (the fact that a claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish obviousness).

Even if there was motivation to combine Hulin with Brooks, again no motivation exists to select an isolated compound encompassed by Formula II in Hulin that the Examiner argues is structurally similar to a compound encompassed by the genus of the claimed invention (nor to replace a hydrogen on such an isolated compound with a non-hydrogen substituent in Brooks to arrive at the claimed invention as the Examiner asserts). "[T]here is nothing in the disclosure of [Hulin or Brooks] suggesting that one should select such variables." *In re Baird*, 16 F.3d at 383. As in the *In re Langer* case, there can be no motivation to select an isolated possibility of a

structurally similar compound absent a showing that Hulin or Brooks distinguishes such <u>isolated</u> possibilities of structurally similar compounds <u>as a class</u> from the plethora of compounds that are not structurally similar- which neither reference does. Moreover, as stated previously, this isolated possibility that the Examiner argues is structurally similar is not in fact structurally similar to any compound covered by the claimed invention. As stated above, the central phenyl moiety in Formula II of Hulin must always be <u>unsubstituted</u> with hydrogen. In contrast, the central phenyl moiety of the claimed invention must always be <u>substituted</u>. Even if there was motivation to combine Hulin with Brooks, some additional motivation or suggestion would be necessary to replace the unsubstituted central phenyl moiety with a substituted central phenyl moiety. That additional motivation does not exist (even when Hulin and Brooks are combined).

Again, more then 95% of the compounds falling under the two generic formulas of Hulin are not even oxazoles. The Examiner can only identify 1 example out of 26 examples disclosed in Hulin (example 13, on page 39 of Hulin that the Examiner argues is structurally similar to the claimed invention [which is not in fact structurally similar for the reasons stated above]). Likewise, Brooks discloses a very broad genus and over 140 examples of species. However, the Examiner only identifies 1 example (example 14, page 83 of Brooks) that she argues is structurally similar to the compounds covered by the claimed invention (which is not structurally similar for the reasons stated above).

In sum: (1) there is no structural similarity between any compound disclosed in Hulin or Brooks and the claimed invention for the reasons stated above; (2) even if the compounds identified by the Examiner in Hulin or Brooks could be considered structurally similar, no motivation exists to select such compounds and then modify them to arrive at the claimed invention for the reasons stated above; and (3) furthermore, there is a lack of motivation to combine Hulin with Brooks for the reasons stated above.

Accordingly, for all of the above reasons, the Applicants respectfully submit that claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52, and 53 are not obvious under 35 U.S.C. § 103; and respectfully request that the Board direct the Examiner to allow such claims.

2. Objection

A. Claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49

Claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49 are objected to by the Examiner as being dependent upon a rejected base claim but would otherwise be allowable by the Examiner if rewritten in independent form. Since the Applicants believe that all the corresponding base claims were improperly rejected for the reasons stated above, the Applicants respectfully submit that claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49 were improperly objected to by the Examiner as being dependent upon a rejected base claim, and respectfully request that the Board direct the Examiner to allow such claims.

VIII. CONCLUSION

In view of the foregoing arguments and the facts of record, the Appellants' respectfully submit that claims 1-50, 52 and 53 are in condition for allowance and respectfully request that the Board direct the Examiner to allow such claims.

An oral hearing is desired and will be formally requested at the appropriate time pursuant to 37 C.F.R. § 41.47(b). No other fee is believed to be due in connection with the filing of this Appeal Brief other than the fees noted above and submitted concurrently herewith. However, if any other fee is deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

Attorney for Appellants

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217782



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

Technology Center: 1600

Adams et al.

Art Unit: 1626

Application No.: 10/700,417

Attorney Docket No.: 21477 US

Filed: November 4, 2003

Examiner: Laura Stockton

For:

NOVEL SUBSTITUTED OXAZOLE DERIVATIVES

REQUEST TO CHARGE DEPOSIT ACCOUNT – APPEAL BRIEF

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CLAIMS APPENDIX

CLAIMS APPENDIX

1. (Original) A compound of formula (I)

wherein

R¹ is alkyl, fluoro-lower-alkyl, cycloalkyl, bicyclic cycloalkyl, or tricyclic cycloalkyl;

R² is hydrogen, lower-alkyl, or fluoro-lower-alkyl;

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, hydroxy, halogen, lower-alkyl, fluoro-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl,

alkyl, lower-alkoxy, fluoro-lower-alkoxy, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkoxy, and lower-alkenyl, wherein at least one of R³, R⁴, R⁵, or R⁶ is not

hydrogen, or

R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S-,

-S-CH=CH-, -CH=CH-O-, -O-CH=CH-, -CH=CH-CH=CH-, -O-(CH₂)₂₋₃-,

-(CH₂)₂₋₃-O-, or -(CH₂)₃₋₅-, and R^5 and R^6 are as defined above,

R⁷ is lower-alkyl, fluoro-lower-alkyl, lower-alkenyl, aryl, or aryl-lower-alkyl;

R⁸ is hydrogen or lower-alkyl;

n is 1, 2 or 3;

or pharmaceutically acceptable salts or pharmaceutically acceptable esters thereof.

2. (Original) The compound according to claim 1, wherein R¹ is lower-alkyl, fluoro-lower-alkyl, cycloalkyl, bicyclic cycloalkyl, or tricyclic cycloalkyl.

- 3. (Original) The compound according to claim 1, wherein R¹ is lower-alkyl or cycloalkyl.
- 4. (Original) The compound according to claim 1, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.
 - 5. (Original) The compound according to claim 1, wherein R² is lower-alkyl.
 - 6. (Previously presented) The compound according to claim 1, wherein R² is methyl.
- 7. (Original) The compound according to claim 6, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.
- 8. (Original) The compound according to claim 1, wherein R³, R⁴, R⁵, and R⁶ independently from each other are hydrogen, halogen, lower-alkyl, or lower-alkoxy, wherein at least one of R³, R⁴, R⁵, or R⁶ is not hydrogen; or R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S- or -CH=CH-CH=CH-, and R⁵ and R⁶ are hydrogen.

9. (Original) The compound according to claim 1, wherein R^3 , R^4 , R^5 , and R^6 independently from each other are hydrogen or lower-alkyl, wherein at least one of R^3 , R^4 , R^5 , or R^6 is not hydrogen.

- 10. (Original) The compound according to claim 1, wherein R³, R⁴, R⁵, and R⁶ independently from each other are hydrogen or methyl, wherein at least one of R³, R⁴, R⁵, or R⁶ is not hydrogen.
- 11. (Original) The compound according to claim 10, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.
 - 12. (Previously presented) The compound according to claim 11, wherein R² is methyl.
- 13. (Original) The compound according to claim 1, wherein R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S- or -CH=CH-CH=CH-, and R⁵ and R⁶ are hydrogen.
- 14. (Original) The compound according to claim 13, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.
 - 15. (Previously presented) The compound according to claim 14, wherein \mathbb{R}^2 is methyl.

16. (Original) The compound according to claim 1, wherein R⁷ is lower-alkyl or lower-alkenyl.

- 17. (Original) The compound according to claim 1, wherein R⁷ is ethyl, n-propyl, i-propyl, or but-3-enyl.
- 18. (Original) The compound according to claim 17, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.
 - 19. (Previously presented) The compound according to claim 18, wherein R² is methyl.
- 20. (Original) The compound according to claim 19, wherein R³, R⁴, R⁵, and R⁶ independently from each other are hydrogen or methyl, wherein at least one of R³, R⁴, R⁵, or R⁶ is not hydrogen.
- 21. (Original) The compound according to claim 19, wherein R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S- or -CH=CH-CH=CH-, and R⁵ and R⁶ are hydrogen.
 - 22. (Previously presented) The compound according to claim 1, wherein R^{8} is hydrogen.
- 23. (Original) The compound according to claim 22, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.

24. (Previously presented) The compound according to claim 23, wherein R² is methyl.

- 25. (Original) The compound according to claim 24, wherein R³, R⁴, R⁵, and R⁶ independently from each other are hydrogen or methyl, wherein at least one of R³, R⁴, R⁵, or R⁶ is not hydrogen.
- 26. (Original) The compound according to claim 25, wherein R⁷ is ethyl, n-propyl, i-propyl, or but-3-enyl.
- 27. (Original) The compound according to claim 24, wherein R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S- or -CH=CH-CH=CH-, and R⁵ and R⁶ are hydrogen.
- 28. (Original) The compound according to claim 27, wherein R⁷ is ethyl, n-propyl, i-propyl, or but-3-enyl.
 - 29. (Original) The compound according to claim 1, wherein n is 1 or 2.
 - 30. (Original) The compound according to claim 1, wherein n is 2.
- 31. (Original) The compound according to claim 30, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.
 - 32. (Previously presented) The compound according to claim 31, wherein R² is methyl.

33. (Original) The compound according to claim 32, wherein R³, R⁴, R⁵, and R⁶ independently from each other are hydrogen or methyl, wherein at least one of R³, R⁴, R⁵, or R⁶ is not hydrogen.

- 34. (Original) The compound according to claim 33, wherein R⁷ is ethyl, n-propyl, i-propyl, or but-3-enyl.
 - 35. (Original) The compound according to claim 34, wherein R⁸ is hydrogen.
- 36. (Original) The compound according to claim 32, wherein R^3 and R^4 are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R^3 and R^4 together are -CH=CH-S- or -CH=CH-CH=CH-, and R^5 and R^6 are hydrogen.
- 37. (Original) The compound according to claim 36, wherein R⁷ is ethyl, n-propyl, i-propyl, or but-3-enyl.
 - 38. (Original) The compound according to claim 37, wherein \mathbb{R}^8 is hydrogen.

39. (Previously presented) A compound of formula (Ic)

$$R^{1} \xrightarrow{O \qquad R^{2}} R^{3} \xrightarrow{R^{4}} O \xrightarrow{O \qquad R^{7}} R^{8} \qquad (Ic)$$

wherein

R¹ is alkyl, fluoro-lower-alkyl, cycloalkyl, bicyclic cycloalkyl, or tricyclic cycloalkyl;

R² is hydrogen, lower-alkyl, or fluoro-lower-alkyl;

R³, R⁴, R⁵, and R⁶ are independently selected from the group consisting of hydrogen, hydroxy,

halogen, lower-alkyl, fluoro-lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, lower-alkoxy, fluoro-lower-alkoxy, hydroxy-lower-alkoxy, lower-alkoxy-lower-alkoxy, and lower-alkenyl, wherein at least one of R^3 , R^4 , R^5 , or R^6 is not hydrogen, or

R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S-,

-S-CH=CH-, -CH=CH-O-, -O-CH=CH-, -CH=CH-CH=CH-, -O-(CH $_2$) $_2$ -3-,

-(CH₂)₂₋₃-O-, or -(CH₂)₃₋₅-, and R^5 and R^6 are as defined above,

R⁷ is lower-alkyl, fluoro-lower-alkyl, lower-alkenyl, aryl, or aryl-lower-alkyl;

R⁸ is hydrogen or lower-alkyl;

n is 1, 2 or 3;

or pharmaceutically acceptable salts or pharmaceutically acceptable esters thereof.

40. (Original) The compound according to claim 39, wherein R¹ is t-butyl, 2,2-dimethyl-propyl, cyclopropyl, or cyclohexyl.

41. (Previously presented) The compound according to claim 39, wherein R² is methyl.

- 42. (Original) The compound according to claim 39, wherein R³, R⁴, R⁵, and R⁶ independently from each other are hydrogen or methyl, wherein at least one of R³, R⁴, R⁵, or R⁶ is not hydrogen.
- 43. (Original) The compound according to claim 39, wherein R⁷ is ethyl, n-propyl, i-propyl, or but-3-enyl.
 - 44. (Original) The compound according to claim 39, wherein R⁸ is hydrogen.
- 45. (Original) The compound according to claim 39, wherein R³ and R⁴ are bonded to each other to form a ring together with the carbon atoms to which they are attached, and R³ and R⁴ together are -CH=CH-S- or -CH=CH-CH=CH-, and R⁵ and R⁶ are hydrogen.
- 46. (Original) The compound according to claim 39, wherein R⁷ is ethyl, n-propyl, i-propyl, or but-3-enyl.
 - 47. (Original) The compound according to claim 39, wherein R⁸ is hydrogen.
- 48. (Original) The compound according to claim 1, selected from the group consisting of (S)-3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-naphthalen-1-yl}-2-ethoxy-propionic acid,

(S)-2-But-3-enyloxy-3-{4-[2-(2-tert-butyl-5-methyl-oxazol-4-yl)-ethoxy]-naphthalen-1-yl}-propionic acid,

3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-naphthalen-1-yl}-2-isopropoxy-propionic acid,

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-naphthalen-1-yl}-2-propoxy-propionic acid, and

3-(4-{2-[2-(2,2-Dimethyl-propyl)-5-methyl-oxazol-4-yl]-ethoxy}-naphthalen-1-yl)-2-propoxy-propionic acid,

or pharmaceutically acceptable salts or pharmaceutically acceptable esters thereof.

49. (Original) The compound according to claim 1, selected from the group consisting of 3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-2-isopropoxy-propionic acid,

3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-2-ethoxy-propionic acid,

3-{4-[2-(2-Cyclopropyl-5-methyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-2-propoxy-propionic acid, and

3-{4-[2-(2-Cyclopropyl-5-methyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-2-ethoxy-propionic acid,

or pharmaceutically acceptable salts or pharmaceutically acceptable esters thereof.

50. (Original) The compound according to claim 1, selected from the group consisting of 3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-3-methyl-phenyl}-2-isopropoxy-propionic acid, and

[rac]-3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid,

or pharmaceutically acceptable salts or pharmaceutically acceptable esters thereof.

51. (Withdrawn) A process for the manufacture of the compound according to claim 1, which process comprises removing a protecting group in a compound of formula (II)

wherein PG is a protecting group.

- 52. (Original) A compound manufactured by the process according to claim 51.
- 53. (Original) A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier and/or adjuvant.
- 54. (Withdrawn) A method for the treatment and/or prevention of a disease modulated by PPARα and/or PPARγ agonists comprising administering, to a mammal in need thereof, a pharmaceutically effective amount of a compound of claim 1.
- 55. (Withdrawn) The method according to claim 54, wherein the disease is diabetes, non-insulin dependent diabetes mellitus, elevated blood pressure, increased lipid and cholesterol levels,

atherosclerotic diseases, metabolic syndrome, endothelial dysfunction, procoagulant state, dyslipidemia, polycystic ovary syndrome, inflammatory diseases or proliferative diseases.

56. (Withdrawn) The method according to claim 54, wherein the disease is non-insulin dependent diabetes mellitus.

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(30) Priority data: 537,673 14 June 1990 (14.06.90)	1	(74) Agents: LUMB, J., Trevor et al.; Pfizer Inc., Eastern Point Road, Groton, CT 06340 (US).				
(60) Parent Application or Grant (63) Related by Continuation US 537 Filed on 14 June 1990 (71) Applicant (for all designated States except US): INC. [US/US]; Eastern Point Road, Groton, (US).	(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US. Published With international search report.					
(54) Title: 3-ARYL-2-HYDROXYPROPIONIC ACI	ID DEF	IVATIVES AND ANALOGS AS HYPOGLYCEMIC AGENTS				
(57) Abstract						
Certain 3-(phenyl, chroman-2-yl, benzofuran-5-yl or benzoxazole-5-yl)-2-(hydroxy or mercapto)propionic acid derivatives and analogs are useful as hypoglycemic and hypocholesterolemic agents.						

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3-ARYL-2-HYDROXYPROPIONIC ACID DERIVATIVES AND ANALOGS AS HYPOGLYCEMIC AGENTS

Background of the Invention

The present invention relates to certain compounds of the formulas (I) and (II), depicted below, having utility as hypoglycemic and hypocholesterolemic agents, methods for their use and pharmaceutical compositions

containing them. In spite of the early discovery of insulin and its subsequent wide-spread use in the treatment of diabetes, and the later discovery and use of sulfonylureas (e.g. chlorpropamide, tolbutamide, acetohexamide, tolazamide) and biguanides (e.g. phenformin) as oral hypoglycemic agents, the treatment The use of of diabetes remains less than satisfactory. insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type I diabetes, insulin dependent diabetes mellitus), requires multiple daily doses, usually by self 20 injection. Determination of the proper dosage of insulin requires frequent estimations of the sugar in The administration of an the urine or in the blood. excess dose of insulin causes hypoglycemia, with effects ranging from mild abnormalities in blood 25 glucose or coma, or even death. Treatment of non-insulin dependent diabetes mellitus (Type II diabetes) usually consists of a combination of diet, exercise, oral agents, e.g., sulfonylureas, and in more severe cases, insuin. However, the clinically available hypoglycemics are unfortunately fraught with 30 other toxic manifestations which limit their use.

any event, where one of these agents may fail in an individual case, another may succeed. A continuing

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need for hypoglycemic agents, which may be less toxic or succeed where others fail, is clearly evident.

Furthermore, atherosclerosis, a disease of the arteries, is recognized to be the leading cause of death in the United States and Western Europe. pathological sequence leading to atherosclerosis and occlusive heart disease has been described in detail by Ross and Glomset in New England Journal of Medicine 295, 369-377 (1976). The earliest stage in this sequence is the formation of "fatty streaks" in the carotid, coronary and cerebral arteries and in the These lesions are yellow in color due to the presence of lipid deposits found principally within smooth-muscle cells and in macrophages of the intima layer of the arteries and aorta. Cholesterol and cholesteryl ester account for most of this lipid. Further, it is postulated that most of the cholesterol found within the fatty streaks results from uptake from These fatty streaks, in turn, give rise to development of the "fibrous plaque", which consists of accumulated intimal smooth muscle cells laden with lipid and surrounded by extra cellular lipid, collagen, elastin and proteoglycans. The cells plus matrix form a fibrous cap that covers a deeper deposit of cell debris and more extracellular lipid. The lipid is primarily free and esterified cholesterol. The fibrous plaque forms slowly, and is likely in time to become calcified and necrotic, advancing to the "complicated lesion" which accounts for the the arterial occlusion and tendency toward mural thrombosis and arterial muscular spasm that characterize advanced atherosclerosis.

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Epidemiological evidence has firmly established hyperlipidemia as a primary risk factor in causing cardiovascular disease (CVD) due to atherosclerosis. In recent years, leaders of the medical profession have placed renewed emphasis on lowering plasma cholesterol levels, and low density lipoprotein cholesterol in particular, as an essential step in prevention of CVD. The upper limits of "normal" are now known to be significantly lower than heretofore appreciated. result, large segments of Western populations are now realized to be at high risk for development or progression of CVD because of this factor. Individuals who possess independent risk factors in addition to hyperlipidemia are at particularly high risk. independent risk factors include glucose intolerance, left ventricular hypertrophy hypertension, and being of the male sex. Cardiovascular disease is especially prevalent among diabetic subjects, at least in part because of the existence of multiple independent risk factors. Successful treatment of hyperlipidemia in the general population, and in diabetic subjects in particular, is therefore of exceptional medical importance.

The first step in recommended therapeutic regimens for hyperlipidemia is dietary intervention. While diet alone produces adequate response in some individuals, many others remain at high risk and must be treated further by pharmacological means. New drugs for the treatment of hyperlipidemia are, therefore, of great potential benefit for large numbers of individuals at high risk of developing CVD. Further, successful treatment of both the hyperlipidemia and hyperglycemia

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associated with the diabetic state with a single therapeutic agent is particularly desirable.

In addition to the hypoglycemic agents cited above, a variety of other compounds have been reported to possess this type of activity, as reviewed by Blank [Burger's Medicinal Chemistry, Fourth Edition, Part II, John Wiley and Sons, N.Y. (1979), pp. 1057-1080].

Schnur, in U.S. Patents 4,342,771, 4,367,234 and 4,617,312, discloses various hypoglycemic oxazolidine-2,4-diones and thiazolidine-2,4-diones substituted at the 5-position with aryl or heteroaryl groups.

Kawamatsu et al., U.S. Patent 4,340,605, disclose hypoglycemic thiazolidine-2,4-dione compounds of the formula

$$\begin{array}{c}
L^1 \\
R^{d} - C - R^{e} - 0
\end{array}$$
NH

wherein R^e is a bond or lower alkylene and when R^d is an optionally substituted five- or six-membered heterocyclic group including one or two hetero-atoms selected from N, O and S, L¹ and L² may each be defined as hydrogen. See also Sohda et al., Chem., Pharm. Bull. Japan, Vol. 30, pp. 3580-3600 (1982).

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Eggler et al., U.S. Patent 4,703,052, disclose hypoglycemic thiazolidinediones of the formula

where the dotted line represents an optional bond, R^f is H, methyl or ethyl, X^b is O, S, SO, SO₂, CH₂, CO, CHOH or NR^k, R^k is H or an acyl group and the numerous definitions of R^g, R^h, Rⁱ and R^j include R^g, R^h and Rⁱ as hydrogen or methyl and R^j as optionally substituted phenyl, benzyl, phenethyl or styryl. EP 283,035A and EP 299,620A describe structurally related benzoxazole and benzofuran derivatives as antidiabetic agents.

Clark et al., in published World patent applications WO89/08650, WO89/8651 and WO89/08652 disclose hypoglycemic thiazolidinediones which collectively include compounds of the type:

wherein ---- represents a bond or no bond; W is O, CO, CH_2 , CHOH, or -CH=CH-; s is 0, 1 or 2; X^a is S, O, NR^a , -CH=CH-, -CH=N- or -N=CH-; and Y^a is CH or N.

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Summary of the Invention

The present invention is directed to compounds having the formulas

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$$z \xrightarrow{\chi^{2}} x \xrightarrow{\text{Coy}^{1}} \cdots (1)$$

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and

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$$z \xrightarrow{\chi}_{\mathbb{Z}^1}^{\text{CCH}_2)_{\mathbb{R}}} \mathbb{Q}^{\text{COY}^1} \xrightarrow{---(\text{II})}$$

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wherein A is

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or

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n is 0 or 1; m is 0, 1 or 2;

--- represents a bond or no bond;

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R is (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_3-C_8) alkenyl, (C_3-C_8) alkynyl, phenyl, (C_7-C_8) phenylalkyl, (C_2-C_8) alkanoyl, or one of said groups mono- or disubstituted with (C_1-C_3) alkyl, trifluoromethyl, hydroxy, (C_1-C_3) alkoxy, fluoro or chloro;

W is 0, CO, CH₂, CHOH or -CH=CH-; X is S, 0, NR², -CH=CH-, -CH=N- or -N=CH-; R² is hydrogen, (C₁-C₃)alkyl, phenyl or benzyl; Y is CH or N;

Z is H, amino, (C_1-C_7) alkyl, (C_3-C_7) cycloalkyl, phenyl, or phenyl mono- or disubstituted with (C_1-C_3) alkyl, trifluoromethyl, (C_1-C_3) alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

 z^1 is hydrogen or (C_1-C_3) alkyl;

 x^1 is 0, s, so or so_2 ; and

 y^1 is hydroxy, (C_1-C_3) alkoxy, phenoxy, benzyloxy, amino, (C_1-C_4) alkanoylamino, (C_1-C_4) alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di[(C_1-C_3) alkyl] aminosulfonylamino, or one of said groups mono- or disubstituted with (C_1-C_3) alkyl, trifluoromethyl, hydroxy, (C_1-C_3) alkoxy, fluoro or chloro;

the pharmaceutically-acceptable cationic salts thereof when $\mathbf{Y}^{\mathbf{l}}$ is hydroxy; and

the pharmaceutically-acceptable acid addition salts thereof when the compound contains a basic nitrogen atom.

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In the preferred compounds, the dotted line (----) represents no bond. The preferred values of A are

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The preferred values of W are O or CO. In their preferred values, X, Y, Z and Z¹ are taken in such manner as to form a 5-methyl-2-phenyloxazol-4-yl group.

In those compounds in which ---- is not a bond, the carbon atom substituted by X¹R and COY¹ is asymmetric, such that these compounds can be either racemic or optically active. Resolution of a racemic form into a pair of optically active enantomers is exemplified below, and the present invention is not to be narrowly construed as limited to the racemic form of these compounds. Similarly, those compounds of the formula (I) wherein the group A contains a saturated ring possess an asymmetric carbon at position 2; and those compounds of the formula (II) contain an asymmetric carbon when W is CHOH.

The expression "pharmaceutically-acceptable cationic salts" is intended to define but not limited to such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine

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(N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine),
benethamine (N-benzylphenethylamine) diethylamine,
piperazine, tromethamine (2-amino-2-hydroxymethyl1,3-propanediol) and procaine. An especially preferred
such salt is the sodium salt.

The expression "pharmaceutically-acceptable acid addition salts" is intended to define but not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

Also embraced by the present invention are pharmaceutical compositions for use in treating a hyperglycemic mammal or a hypercholesterolemic mammal which comprises a blood glucose lowering amount or a blood cholesterol lowering amount of a compound of formula (I) or (II) and a pharmaceutically-acceptable carrier. The invention further comprises a method of lowering blood glucose in a hyperglycemic mammal which comprises administering to said mammal a blood glucose lowering effective amount of a compound of formula (I) or (II); and a method of lowering blood cholesterol in a hypercholesterolemic mammal which comprises administering to said mammal a blood cholesterol lowering amount of a compound of the formula (I) or (II).

Detailed Description of the Present Invention

The compounds of the formulas (I) and (II) of the present invention are readily prepared using conventional chemical processes. In the discussion which follows, the radical R' is defined as follows:

and

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wherein m, A, W, X, Y, Z and Z^1 are as defined above.

When the dotted line (----) represents a bond, the compounds of the formula (I) or (II) wherein \mathbf{Y}^1 is hydroxy and \mathbf{X}^1 is S are generally prepared from the corresponding aldehyde by the two step sequence:

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R'CHO
$$\longrightarrow$$
 R'CH \longrightarrow R'CH $=$ \swarrow SR (CH)

The first step of this sequence is accomplished by condensation of the aldehyde (A) with thiazolidine-4-one-2-thione (rhodanine) in the presence of a

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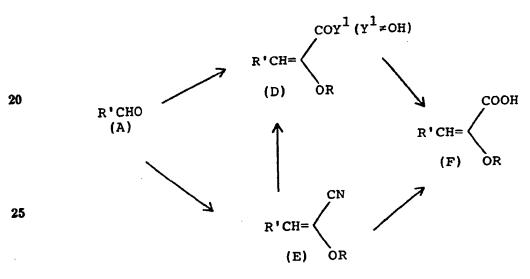
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secondary amine such as piperidine or pyrrolidine in a reaction inert solvent such as ethanol at a temperature in the range of about 40-100°C, conveniently at the reflux temperature of the reaction.

As used above and elsewhere herein, the expression "reaction inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

When the dotted line (---) represents a bond, the compounds of the formula (I) or (II) wherein x^1 is 0 are generally prepared by condensation of the above aldehyde (A) with a suitably substituted acetic acid derivative, for example,



The condensation step is conveniently carried out by irreversibly converting the acrylic acid derivative, $\text{CH}_2 = \text{COR-CN}$ or $\text{CH}_2 = \text{COR-COY}^1$ (in which Y^1 is other than OH), to the sodium salt by the action of NaH in a reaction-inert solvent such as dimethylformamide, generally done at a temperature in the range of about

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25-60°C, and then adding the aldehyde and further reacting, generally at a somewhat higher temperature, e.g., 50-100°C.

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If the condensation product is an ester or an amide (D), it can, if desired, be conventionally hydrolyzed, preferably under aqueous basic conditions, to the acid. If the condensation product is a nitrile, it can be conventionally converted to ester, amide or acid, as desired. Specifically exemplified below is the conversion of nitrile to carboxamide, from which both of the expected (E) and (Z) isomers about the double bond are isolated.

The compounds (C) and (F) are further converted to compounds in which Y is other than hydroxy by conventional transformations according to which acids are converted to esters, amides and imides. Furthermore, the double bond in such compounds can be conventionally reduced to form compounds of the formulas (I) and (II) wherein the dotted line (----) represents no bond. For example, reduction of the double bond is accomplished by conventional hydrogenation over a noble metal catalyst such as Pd/C, Rh/C or Rh(Ph3P)3Cl in a reaction inert solvent such as ethanol generally at temperatures in the range of ambient to 80°C, preferably at moderate pressures, e.g., up to about 125 psig so as not to require expensive and complex high pressure hydrogenation apparatus. However, the presently preferred routes to compounds of the formulas (I) and (II) wherein --- represents no bond are as detailed below.

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Compounds of the formulas (I) and (II) wherein the dotted line (----) represents no bond and x^1 is S are generally prepared from the corresponding amine via a two- or three-step reaction sequence:

e.g.
$$R'NH_2 \longrightarrow R' \xrightarrow{X^2} CN \longrightarrow R' \xrightarrow{SR} CN$$

(G)
$$(H) \qquad (K) \qquad (K) \qquad (K) \qquad (K) \qquad (COOR^1) \qquad (COOR^1)$$

wherein R, R' and Y¹ are as defined above, X² is a nucleophilically displacable group such as I, Cl, Br or OSO₂CH₃, and R¹ is an ester forming group such as (C₁-C₃)alkyl. According to this sequence, the amine (G) is first conventionally diazotized (e.g. with NaNO₂/conc.HBr or t-butyl nitrite) in the presence of a copper (II) salt and acrylonitrile or an acrylate ester to form the nitrile (H) or ester (J). This is followed by convention nucleophilic displacement of the group X² with RS, with or without conventional concurrent hydrolysis of the nitrile or ester. For example, an alpha-bromo ester (J, X²=Br) is reacted with an excess of an alkali metal salt of a mercaptan or thiolcarboxylic acid (greater than two molar

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equivalents) in an aqueous solvent such as aqueous dimethylformamide, usually at an elevated temperature, e.g., in the range of 60-100°C, to form the acid:

R' COOH

On the other hand, the nitrile or ester group is retained intact by reacting a compound (H) or (J) with a mercaptan or thiolcarboxylic acid in the presence of a base such as K_2^{CO} in an anhydrous reaction inert solvent such as dimethylformamide, generally at lower temperatures, e.g., in the range of about 15-45°C. Prior to or after nucleophilic displacement, nitrile groups are converted to desired groups -COY¹ by conventional methods. For example, compounds wherein y^1 is alkoxy are obtained by contacting the nitrile with dry HCl in an excess of the corresponding alkanol, a reaction usually carried out without additional solvent at a temperature in the range of about 15-45°C.

Compounds of the formulas (I) and (II) wherein the dotted line (---) represents no bond and X¹ is O are generally prepared from the corresponding aldehyde according the following reaction sequences:

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$$R' CHO \longrightarrow R' \longrightarrow CCH_{3}$$

$$R' CHO \longrightarrow R' \longrightarrow CR^{2}$$

$$R' \longrightarrow CHO \longrightarrow CHO \longrightarrow CHO$$

$$R' \longrightarrow CHO \longrightarrow CHO$$

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The enol ether (M) is conventionally formed from the aldehyde (A) via the Wittig reaction, using conditions as exemplified in specific examples below. further sequence, the enol ether is conventionally hydrolyzed with aqueous acid to form the aldehyde (N), which in turn is reacted with trimethylsilyl cyanide to form the O-trimethylcyanhydrin (P). The latter is conventionally reacted with an alcohol R¹OH in the presence of anhydrous HCl to form the alpha-hydroxy ester (R). When RO is an ester, e.g., acetoxy, the hydroxyester (R) is readily converted to the ester by the action of the appropriate activated acid, e.g., an acid chloride or mixed anhydride, in the presence of at least one equivalent of a tertiary amine, usually in a reaction inert solvent such as tetrahydrofuran, conveniently at or near ambient temperature. When RO is an ether, e.g., ethoxy, the hydroxy ester (R) is reacted with NaH, under scrupulously anhydrous conditions in a reaction inert solvent such as tetrahydrofuran, so as to irreversibly form the sodium salt. The latter is then coupled with a mesylate ester or halide in typical nucleophilic displacement conditions described above, under the same anhydrous conditions to form the ester (S). Alternatively, under hydrous conditions (with at least one molar equivalent of water present), the latter reaction yields the acid In a second further sequence, the enol ether (M) is reacted under anhydrous conditions with an alcohol R^2OH in the presence of a strong anhydrous acid (e.g., 30 p-toluenesulfonic acid) to form the acetal (0), which, upon reaction with trimethylsilyl cyanide, produces the cyanhydrin derivative (Q). The CN group in the latter compound is conventionally converted to the acid (T),

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e.g. by the action of NaOH in an aqueous solvent, or to the ester (S), e.g., by the action of dry HCl in an excess of an alcohol $R^1\text{OH}$.

Many of the compounds of the present invention are alternatively or preferably prepared from preformed compounds having different values of R, X¹ and Y¹. For example, sulfoxides $(x^1=so)$ are preferably formed from the corresponding sulfide $(X^1=S)$ by the action of substantially one molar equivalent of a peroxyacid, conveniently, m-chloroperbenzoic acid. Sulfones $(x^1=SO_2)$ are also obtained from the corresponding sulfide, but now generally with an excess (at least 2 molar equivalents) of the peracid. These oxidations are generally carried out in a reaction inert solvent such as tetrahydrofuran, at a temperature generally in the range of about 0-40°C. Other transformations conveniently carried out to convert one preformed compound of the formula (I) or (II) to another such compound include esterification of acids, e.g.,

$$-cooh \longrightarrow -cocl \longrightarrow -coor^1$$

conversion of acids to amides or imides, e.g.,

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$$-COOH \longrightarrow -COOH_{2}$$

$$\downarrow 0$$

$$-CONHCR^{1};$$

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and ammonolysis of esters, e.g.,

$$-\text{COOR}^1 \longrightarrow -\text{CONH}_2$$

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Various of these transformations are exemplified below.

It will be readily understood by those skilled in the organic chemical art that in the compounds of the formulas (I) and (II) in which the dotted line (----) represents no bond, the carbon atom bearing the X1R and COY groups is asymmetric and so potentially resolvable into a pair of optically active isomers. Substrates particularly well suited to such resolution are those carboxylic acids of the formulas (I) or (II) wherein Y is OH, e.g., by combining the acid with an optically active amine, and separating the resulting pair of diastereomeric salts by fractional crystallization converting; or by reacting the acid with an optically alcohol or amine, and separating the resulting pair of diastereomeric esters or amides by chromatography or fractional crystallization, followed by hydrolysis of the separated isomers to yield the desired optically active acids. Such a resolution is exemplified below.

The pharmaceutically-acceptable cationic salts of the compounds of the present invention are readily prepared by reacting the acid forms with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium or potassium ethylhexanoate, magnesium oleate), employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be

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otherwise isolated by concentration and/or addition of a non-solvent.

The acid addition salts of the compounds of the present invention are readily prepared by reacting the base forms with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The amines (R'NH₂) and aldehydes (R'CHO), when not commercially available or known in the prior art, are available by conventional synthetic methods, as exemplified below. For example the starting aldehydes are generally available as described in W089/08650, W089/8651 and W089/08652 (cited above), and in U.S. Patent 4,725,610; while the amino compounds are most generally available by reduction of the corresponding nitro compounds, as described in that same U.S. Patent 4,725,610.

The present compounds of the formulas (I) and (II) are readily adapted to clinical use as hypoglycemic or hypocholesterolemic agents. The activity required for this former clinical use is defined by the test for

hypoglycemic effect in ob/ob or db/db mice by the following procedure:

Five to eight week old C57BL/6J-ob/ob or C57BL/K_SJ-db/db mice (obtained from Jackson Laboratory, 5 Bar Harbor, Maine) were housed five per cage under standard animal care practices. After a one week acclimation period, the animals were weighed and 25 microliters of blood was collected via an ocular bleed prior to any treatment. The blood sample was 10 immediately diluted 1:5 with saline containing 2.5 mg/ml sodium fluoride and 2% sodium heparin, and held on ice for metabolite analysis. Animals were then dosed daily for five days with drug (5-50 mg/kg), a positive control (50 mg/kg) of ciglitazone; U.S. 15 Patent 4,467,902; Sohda et al., Chem. Pharm. Bull., vol. 32, pp. 4460-4465, 1984), or vehicle. All drugs were administered in a vehicle consisting of 0.25% w/v methyl cellulose. On day 5, the animals were weighed again and bled (via the ocular route) for blood 20 The freshly collected samples were metabolite levels. centrifuged for two minutes at 10,000 xg at room temperature. The supernatant was analyzed for glucose, for example, by the ABA 200 Bichromatic Analyzer M, using the A-gent m glucose UV reagent system* 25 (hexokinase method) using 20, 60 and 100 mg/dl standards. Plasma glucose was then calculated by the equation, Plasma glucose (mg/dl) = Sample value \times 5 \times 1.67 = 30

8.35 x Sample value

where 5 is the dilution factor and 1.67 is the plasma hematocrit adjustment (assuming the hematocrit is 40%).

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MA registered trademark of Abbott Laboratories, Diagnostics Division, 820 Mission Street, So. Pasadena, CA 91030.

*A modification of the method of Richterich and Dauwalder, Schweizerische Medizinische Wochenschrift, 101, 860 (1971).

The animals dosed with vehicle maintain substantially unchanged hyperglycemic glucose levels (e.g., 250 mg/dl), while positive control animals have depressed glucose levels (e.g., 130 mg/dl). Test compounds are reported in terms of % glucose normalization. For example, a glucose level which is the same as the positive control is reported as 100%.

Studies such as that described below demonstrate that the compounds of formula (I) effect the lowering of serum cholesterol levels in mammals.

Female mice (strain C57Br/cd J), obtained from Jackson Laboratories, Bar Harbor, Maine, are used at age 8-12 weeks, following 2-4 weeks acclimation having free access to water and standard laboratory chow. Animals are divided randomly into three groups of 6-7 animals. All three groups are placed on a diet containing 0.75% cholesterol, 31% sucrose, 15.5% starch, 20% casein, 17% cellulose, 4.5% corn oil, 5% coconut oil, 0.25% cholic acid, 4% salts and 2% vitamin; permitted to feed ad lib for 18 days; and dosed daily at 9-11 a.m. for the final 5 days by oral gavage, the control group with 5 ml/kg of vehicle (0.1% aqueous methyl cellulose) and the test groups with the compound under study at doses ranging from 0.1 to 10 mg/kg/day in vehicle. After the fourth day of dosing, the animals are fasted overnight, starting at 5 p.m. The following morning a fifth and final dose of the

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compound is administered to the test groups and, three hours later, the animals are sacrificed by decapitation. Blood from the body trunk is collected and allowed to clot, and the serum assayed enzymatically, using an Abbott VP automated analyzer, for HDL cholesterol, LDL and VLDL cholesterol, and total cholesterol. Whether judged on the basis LDL + VLDL cholesterol levels, total cholesterol levels or the ratio of LDL + VLDL/HDL, the compounds of this invention generally show favorable result in lowering cholesterol levels.

The present compounds of the formulas (I) and (II) are clinically administered to mammals, including man, via either the oral or the parenteral route. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.10 to about 50 mg/kg body weight of the subject per day, preferably about 0.10 to about 10 mg/kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage. This will vary according to the particular compound employed and with the subject being treated.

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The compounds can be used in pharmaceutical preparations containing the compound, or pharmaceutically acceptable acid salt thereof, in combination with a pharmaceutically-acceptable carrier or diluent. Suitable pharmaceutically-acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described above. Thus, for oral administration the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts of the The injectable solutions prepared in this compounds. manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in

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The present invention is illustrated by the following Examples. However, it should be understood that the invention is not limited to the specific details of these examples. Nomenclature used herein is based on Rigaudy and Klesney, IUPAC Nomenclature of Organic Chemistry, 1979 Ed., Pergammon Press, New York, 1979.

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EXAMPLE 1

3-[4-(2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy)phenyl]-2-methylthio-2-propenoic Acid

4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (Takeda U.S. Patent 4,725,610; 0.5 g,
1.6 mmol'), rhodanine (0.21 g, 1.6 mmol) and piperidine
(5 drops) were combined in ethanol (10 ml) and heated
to reflux for 2 hours. The mixture was cooled and the
precipitate filtered (0.35 g, mp 202.5-203.5°C). A
slurry of this compound (0.25 g, 0.58 mmol) in 15%
sodium hydroxide (5 ml) was heated to gentle reflux for
1 hour, then cooled and treated with a solution of
methyl iodide (0.16 ml, 2.6 mmol) in methanol (5 ml).
After 2 hours stirring at room temperature, the mixture
was diluted with ice-water and acidified with 2N hydrochloric acid. The precipitate was filtered and
recrystallized from 1:1 ethanol-water (10 ml) (0.11 g,
mp 178.5-182°C).

Starting from the same aldehyde and using propyl iodide as the reagent, 3-[4-(2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy)phenyl]-2-propylthio-2-propenoic acid was prepared by the same method (gummy solid).

Starting from 4-[3-(5-methyl-2-phenyl-4-oxazolyl)-propionyl]benzaldehyde (WO89/08650), 3-[4-(3-(5-methyl-2-phenyl-4-oxazolyl)propionyl)phenyl]-2-methylthio-2-propenoic acid was prepared by the same method (mp 150-152°C).

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EXAMPLE 2

3-[4-(2-(5-Methyl-2-phenyl-4-oxazolyl)phenyl]-2-(methylthio)propanoic Acid

To a solution of 4-[2-(5-methyl-2-phenyl-4oxazolyl)ethoxylaniline (U.S. Patent 4,725,610) (3.7 g, 12.6 mmol) in acetone (50 ml) and methanol (50 ml), cooled to 0°C, was added 48% hydrobromic acid (6.2 ml, 54 mmol), and after 5 minutes a solution of sodium nitrite (1.0 g, 15 mmol) in water (5 ml), dropwise, keeping the temperature below 5°C. After 15 minutes ethyl acrylate (8.6 ml, 79 mmol) was added dropwise, the mixture was warmed to 38°C and cuprous oxide (0.42 g, 2.9 mmol) was added. The solution was stirred 1 hour at 40°C, then concentrated, diluted with aqueous ammonia and extracted with ethyl acetate $(3 \times 30 \text{ ml})$. The combined extracts were washed with water (2 x), brine, dried over magnesium sulfate and concentrated. The product, ethyl alpha-bromo-4-[2-(5-methyl-2phenyl-4-oxazolyl)ethoxy]benzenepropanoate, was isolated by flash chromatography (hexane/ethyl acetate, 4:1) as a yellow oil (1.17 g).

To a solution of ethyl alpha-bromo-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate (0.20 g, 0.44 mmol) in dimethylformamide (0.5 ml) was added a solution of sodium thiomethoxide (0.10 g, 1.4 mmol) in water (0.3 ml). The resulting solution was stirred at 80°C for 16 hours. Water was added the mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate (2 x). The combined extracts were washed with water (5 x) and brine, dried over magnesium sulfate and concentrated to a yellow oil. The product was purified by flash-chromatography

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(hexane/ethyl aceate, 2:1) and obtained as a yellow gum (60 mg).

 $1_{\rm H}$ NMR (CDCl $_3$, 300 MHz) delta 2.19 (s, 3H), 2.36 (s, 3H), 2.88 (dd, J = 6Hz, 14Hz, 1H), 2.96 (t, J = 7Hz, 2H), 3.16 (dd, J = 9Hz, 14Hz, 1H), 3.41 (dd, J = 6Hz, 9Hz, 1H), 4.13 (t, J = 7Hz, 2H), 6.78 (d, J = 8Hz, 2H), 7.11 (d, J = 8Hz, 2H), 7.39-7.41 (m, 3H), 7.92-7.96 (m, 2H).

EXAMPLE 3

Ethyl 3-[4-(2-(5-Methyl-2-phenyl-4-oxazolyl)-ethoxy)phenyl]-2-(acetylthio)propanoate

To a solution of ethyl alpha-bromo-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate (0.18 g, 0.38 mmol) and thiolacetic acid (75 μ l, 1.05 mmol) in dimethylformamide (2 ml) was added potassium carbonate (0.15 g, 1.05 mmol). After stirring overnight at room temperature, the mixture was poured into water and acidified with 1N hydrochloric acid, then extracted with ethyl acetate (3 x). The combined extracts were washed with water (5 x) and brine, dried over magnesium sulfate and concentrate to a yellow oil (0.11 g).

1_{H NMR} (CDCl₃, 300 MHz) delta 1.18 (t, J = 7Hz,
3H), 2.31 (s, 3H), 2.37 (s, 3H), 2.91-2.99 (m, 1H),
25 2.97 (t, J = 7Hz, 2H), 3.13 (dd, J = 8Hz, 14Hz, 1H),
4.10 (q, J = 7Hz, 2H), 4.21 (t, J = 7Hz, 2H), 4.36 (dd,
J = 7Hz, 8Hz, 1H), 6.80 (d, J = 8Hz, 2H), 7.09 (d, J =
8Hz, 2H), 7.38-7.42 (m, 3H), 7.94-7.98 (m, 2H).

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EXAMPLE 4

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(propylthio)propanoate

A. alpha-(5-Methyl-2-phenyl-4-oxazolyl)-5-nitro-2-benzofuranmethanol

A solution of 4-bromoacetyl-5-methyl-2-phenyloxazole (Takeda U.S. Patent 4,725,610) (53 g, 0.19 mol), 5-nitrosalicyladehyde (32 g, 0.19 mol) and diisopropylethylamine (66 ml, 0.38 mol) in dimethylformamide (250 ml) was heated to 91-94°C for 3 hours. The mixture was cooled, diluted with ethyl acetate (300 ml) and the solid was collected. This solid was washed with chloroform (2 x 100 ml) and dried (56 g, mp It was then placed in tetrahydrofuran 233-234°C). (600 ml) and methanol (300 ml) and the slurry was cooled to 0°C. Sodium borohydride (9.1 g, 0.24 mol) was added portion-wise over 1 hour and the cloudy solution was stirred at 0°C for 2 hours. The bulk of the solvent was removed in vacuo and water (700 ml) was The mixture was acidified with 6N hydrochloric acid and stirred for 30 minutes. The yellow-tan solid was collected, washed with water and dried (57 g, mp 166-167°C).

B. 5-Amino-2-(5-methyl-2-phenyl-4-oxazolyl) - methylbenzofuran

alpha-(5-Methyl-2-phenyl-4-oxazolyl)-5-nitro-2-benzofuranmethanol (57 g, 0.16 mol) was dissolved in trifluoroacetic acid (350 ml), while cooling to 0°C. Triethylsilane (64 ml, 0.40 mol) was added. The solution was stirred 1.5 hours at 0°C and overnight at room temperature. The solution was concentrated to near-dryness and the residue dissolved in ethyl acetate (750 ml). This solution was washed with water. The

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precipitate formed during the wash was collected. organic solution was washed with satured sodium bicarbonate, during which more precipitate formed and The ethyl acetate phase of the filtrate was collected. was washed again with saturated sodium bicarbonate, then with brine, dried over sodium sulfate and concentrated. The residue was triturated with isopropyl ether and a solid was obtained. The combined solids obtained hereabove (51 g, 0.15 mol) were placed in a Parr bottle together with platinum oxide (3 g) and ethyl acetate (1.5 1) and hydrogenated at 40 psi for 1.25 hours. The catalyst was filtered through Celite, and after washing the filtering pad with more ethyl acetate, the solvent was removed in vacuo to give a yellow residue which was triturated with isopropyl ether (200 ml). The pale yellow solid was collected (37.1 g, mp 161.5-162.5°C).

C. alpha-Chloro-2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranpropanenitrile

To a solution of acrylonitrile (11.2 ml, 0.17 mol) and tert-butyl nitrite (21.4 ml, 0.18 mmol) in acetonitrile (16 ml) was added cupric chloride (19.4 g, 0.14 mol), and 5-amino-2-(5-methyl-2-phenyl-4-oxazolyl)methylbenzofuran (37 g, 0.12 mol) portionwise over 40 minutes. The mixture was stirred for 30 minutes then poured into 20% hydrochloric acid (500 ml) and this solution was extracted with ethyl acetate (2 x 700 ml). The combined extracts were washed with 20% hydrochloric acid (2 x 250 ml), and brine (350 ml), dried over sodium sulfate and concentrated. The thick gum was extracted with boiling hexane (4 x 450 ml), the combined liquid phases were decanted, boiled down to

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ca. 1100 ml and cooled. The solid was collected (6.9 g). The mother liquor was concentrated and the residue was purified by flash-chromatography (hexanes/ethyl acetate, 4:1) to give a yellow solid which was combined with the material obtained from the hot hexane to give 16 g of the title compound as a yellow sticky solid.

Ethyl 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]-2-(propylthio)propanoate

Hydrogen chloride was bubbled into a slurry of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-alpha-chloro-5benzofuranpropanenitrile (16.3 g, 43 mmol) in 95% ethanol (600 ml) at 0°C for 30 minutes, after which the mixture was stirred for 3 days at room temperature. The solvent was removed in vacuo and the residue partitioned between saturated sodium bicarbonate (350 ml) and ethyl acetate (500 ml). The aqueous layer was extracted with ethyl acetate (250 ml), the organic phases were combined, washed with brine, dried over The oily residue was sodium sulfate and concentrated. extracted with boiling hexane (2 x 400 ml), the solution was boiled down to 400 ml and cooled. precipitated solid was collected. The filtrate was boiled down to 250 ml and allowed to cooled overnight The two solids were and the solid was collected. combined (11.5 g, mp 113-115°C).

To a solution of this solid (5 g, 12 mmol) in dimethylformamide (100 ml) was added propyl mercaptan (3.0 gml, 33 mmol), followed by potassium carbonate (4.6 g, 33 mmol). The slurry was stirred at room temperature overnight then poured into water (400 ml), acidified with 6N hydrochloric acid and extracted with

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ethyl acetate (2 x 300 ml). The combined extracts were washed with water (3 x 200 ml) and brine, dried over sodium sulfate and concentrated, leaving a yellow oil (4.3 g).

 $1_{\rm H~NMR}$ (CDCl₃, 300 MHz) delta 0.93 (t, J = 7.5Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H), 1.56 (m, 2H), 2.32 (s, 3H), 2.57 (m, 2H), 2.99 (dd, J = 6.4Hz, 13.9Hz, 1H), 3.22 (dd, J = 9.4Hz, 13.6Hz, 1H), 3.48 (dd, J = 6.4Hz, 9.1Hz, 1H), 3.99 (s, 2H), 4.08 (m, 2H), 6.40 (d, J = 1.1Hz, 1H), 7.03 (dd, J = 1.6Hz, 8.6Hz, 1H), 7.29 (s, 1H), 7.29 (d, J = 7.8Hz, 1H), 7.37-7.42 (m, 3H), 7.96-7.99 (m, 2H).

Using the corresponding mercaptans, the following compounds were prepared by the same procedure:

Ethyl 3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl]-2-(phenylmethylthio)propanoate (oil)

1 H NMR (CDCl₃, 300 MHz) delta 1.20 (t, J = 7Hz,

3H), 2.32 (s, 3H), 2.92 (dd, J = 6Hz, 14Hz, 1H), 3.20
(dd, J = 9Hz, 14Hz, 1H), 3.45 (dd, J = 6Hz, 9Hz, 1H),

3.75 (d, J = 13Hz, 1H), 3.80 (d, J = 13Hz, 1H), 4.0 (s,

2H), 4.05 (m, 2H), 6.38 (s, 1H), 6.90 (dd, J = 2Hz,

8Hz), 7.10-7.30 (m, 7H), 7.35-7.45 (m, 3H), 7.92-8.00

Ethyl 2-ethylthio-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoate (oil)

1 H NMR (CDCl₃, 300 MHz) delta 1.15 (t, J = 7.4Hz,
3H), 1.20 (t, J = 7.7Hz, 3H), 2.32 (s, 3H), 2.61 (dq,
J = 1.4Hz, 7.8Hz, 2H), 3.07 (dd, J = 6.3Hz, 13.8Hz,
1H), 3.23 (dd, J = 9.6Hz, 13.9Hz, 1H), 3.50 (dd, J = 6.3Hz, 9.1Hz, 1H), 3.99 (s, 2H), 4.08 (m, 2H), 6.40 (s, 1H), 7.03 (dd, J = 1.65Hz, 8.6Hz, 1H), 7.29 (s, 1H),
7.29 (d, J = 8.3Hz, 1H), 7.37-7.42 (m, 3H), 7.42-7.99

(m, 2H).

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Ethyl 3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl]-2-(octylthio)propanoate (oil)

1 H NMR (CDCl₃, 300 MHz) delta 0.85 (t, J = 6.5Hz,

3H), 1.18 (t, J = 7.0Hz, 3H), 1.22-1.35 (m, 10H),

1.47-1.58 (m, 2H), 2.33 (s, 3H), 2.58 (m, 2H), 2.99

(dd, J = 6.3Hz, 13.8Hz, 1H), 3.22 (dd, J = 9.2Hz,

13.8Hz, 1H), 3.48 (dd, J = 6.3Hz, 9.2Hz, 1H), 3.99 (s,

2H), 4.08 (m, 2H), 6.40 (s, 1H), 7.03 (dd, J = 1.8Hz,

8.5Hz, 1H), 7.28 (s, 1H), 7.29 (d, J = 7.9Hz, 1H),

7.37-7.42 (m, 3H), 7.95-7.99 (m, 2H).

EXAMPLE 5

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl-2-(propylthio)propanoic Acid

To a solution of title product of Example 4 (3.8 g, 8.2 mmol) in methanol (100 ml) was added lN sodium hydroxide (100 ml). The mixture was heated to reflux for 2 hours, cooled, poured onto ice (300 ml) and acidified with 6N hydrochloric acid, then extracted with ethyl acetate (500 ml), during which some precipitated solid was collected. The aqueous phase was extracted again with ethyl acetate (200 ml), the combined extracts were washed with water (300 ml) and brine (300 ml), dried over sodium sulfate and concentrated, leaving a yellow-orange solid. The

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solids were combined and recrystallized from ethyl acetate (150 ml) to give the title compound as an off-white solid (2.5 g, mp 169-170°C).

The following compounds were prepared by the same route from the corresponding ethyl esters:

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-propanoic acid (mp 153-154°C)

2-Ethylthio-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanoic acid (mp 144-145°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(phenylthio)propanoic acid (mp 160-161°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-(octylthio)propanoic acid (mp 94-96°C)

EXAMPLE 6

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methylbenzofuran-5-yl]-2-(methylthio)propanoic Acid

5-Amino-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]-benzofuran was converted into the title compound according to the procedure of Example 2. Mp 178-179°C.

3-[2-[5-Methyl-2-(3-methylphenyl)-4-oxazolyl]-methyl]benzofuran-5-yl]-2-(methylthio)propanoic acid was prepared by the same procedure using the corresponding starting material. Mp 125-127°C.

EXAMPLE 7

Ethyl 2-(Acetylthio)-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoate was prepared from ethyl alpha-bromo-2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranpropanoic acid according to the procedure of Example 3 and obtained as an oil.

 1 H NMR (CDCl₃, 300 MHz) delta 1.10 (t, J = 7Hz, 3H), 2.29 (s, 3H), 2.34 (s, 3H), 3.04 (dd, J = 7Hz, 14Hz, 1H), 3.25 (dd, J = 8Hz, 14Hz, 1H), 3.99 (s, 2H),

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4.07 (q, J = 7Hz, 2H), 4.38 (dd, J = 7Hz, 8Hz, 1H), 6.40 (s, 1H), 7.03 (dd, J = 2Hz, 8Hz, 1H), 7.28 (s, 1H), 7.36-7.42 (m, 3H), 7.94-7.98 (m, 2H).

Ethyl 2-((Acetylthio)-3-[2-[(5-methyl-2-(3-methylphenyl)-4-oxazolyl)methyl]benzofuran-5-yl]-propanoate was prepared according to the same procedure and obtained as an oil.

1_H NMR (CDCl₃, 300 MHz) delta 1.10 (t, J = 7Hz,
3H), 2.30 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 3.05
(dd, J = 7Hz, 14Hz, 1H), 3.27 (dd, J = 8Hz, 14Hz, 1H),
4.00 (s, 2H), 4.07 (q, J = 7Hz, 2H), 4.39 (dd, J = 7Hz,
8Hz, 1H), 6.40 (s, 1H), 7.04 (dd, J = 2Hz, 8Hz, 1H),
7.18 (d, J = 8Hz, 1H), 7.26-7.30 (m, 3H), 7.75 (d, J =
8Hz, 1H), 7.81 (s, 1H).

EXAMPLE 8

Ethyl 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]-2-(propylsulfinyl)-

propanoate

To a solution of title product of Example 4

(0.39 g, 0.85 mmol) in tetrahydrofuran (75 ml) was added at 0°C, 80% m-chloroperoxybenzoic acid (0.18 g, 0.85 mmol). After 10 minutes, ethyl vinyl ether (0.5 ml) was added and the solution was diluted with ethyl acetate, washed with water (3 x) and brine, dried over magnesium sulfate and concentrated. Flash-chromatography (hexanes/ethyl acetate, 2:1) gave the expected product as an oil (0.35 g).

 1 H NMR (CDCl₃, 300 MHz) delta 1.05 (t, J = 7Hz, 3/2H), 1.09 (t, J = 7Hz, 3/2H), 1.12 (t, J = 7Hz, 3/2H), 1.19 (t, J = 7.1Hz, 3/2H), 1.73-1.94 (m, 2H), 2.34 (s, 3H), 2.56-2.88 (m, 2H), 3.27-3.46 (m, 2H), 3.71-3.78 (m, 1H), 4.01 (s, 2H), 4.05-4.26 (m, 2H),

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6.41 (d, J = 0.7Hz, 1/2H), 6.42 (d, J = 1.0Hz, 1/2H), 7.04 (dd, J = 1.7Hz, 6.9Hz, 1/2H), 7.07 (dd, J = 1.8Hz, 6.7Hz, 1/2H), 7.30-7.33 (m, 2H), 7.36-7.43 (m, 3H), 7.92-8.03 (m, 2H).

EXAMPLE 9

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl]-2-(methylsulfonyl)propionic acid

To a solution of title product of Example 5 (0.30 g, 0.74 mmol) in tetrahydrofuran (75 ml) was added 80% m-chloroperoxybenzoic acid (0.16 g, 0.74 mmol) at 0°C. After 10 minutes, ethyl vinyl ether (0.5 ml) was added, the solution was diluted with ethyl acetate, washed with water (3 x) and brine, dried over magnesium sulfate and concentrated. The product was isolated by flash-chromatography (hexane/ethyl acetate, 1:1) as a yellow solid (0.11 g, mp 220-203°C).

EXAMPLE 10

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)-benzofuran-5-yl]-2-(propylsulfinyl)propanoic Acid

A solution of the title product of Example 8 (0.20 g, 0.42 mmol) in methanol (5 ml) and 1N sodium hydroxide (5 ml) was stirred at room temperature for 48 hours. It was then poured into water, acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x). The combined extracts were washed with water and brine, dried over sodium sulfate and concentrated to an oil. The product was purified by flash-chromatography (ethyl acetate/hexane, 10:1) and obtained as an oily solid (43 mg).

 1 H NMR (CDCl₃, 300 MHz, 62°C) delta 0.88 (t, J = 7Hz, 3/2H), 0.97 (t, J = 7Hz, 3/2H), 1.60 (m, 1H), 1.75 (m, 1H), 2.34 (s, 3/2H), 2.36 (s, 3/2H), 2.55-2.70 (m, 1H), 2.80 (m, 1/2H), 2.91 (m, 1/2H), 3.05 (m,

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1/2H), 3.35 (m, 1H), 3.42-3.51 (m, 1.5H), 3.97 (s, 2/2H), 3.99 (s, 2/2H), 6.34 (s, 1/2H), 6.38 (s, 1/2H), 7.06 (d, J = 7Hz, 1H), 7.20-7.27 (m, 1H), 7.31-7.37 (m, 4H), 7.92-7.95 (m, 2H).

EXAMPLE 11

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl)-2-(methylthio)-N-(phenylsulfonyl) propanamide

A mixture of the title product of Example 6 (0.15 g, 0.37 mmol) and thionyl chloride (0.10 ml, 1.4 mmol) was heated on a steam bath for 20 minutes. mixture was cooled, diluted with benzene and concentrated. A mixture of benzenesulfonamide (0.12 g, 0.74 mmol) and 60% sodium hydride (32 mg, 0.81 mmol) in tetrahydrofuran (5 ml) was heated at reflux for 30 minutes, cooled to 0°C and treated with a solution of this acid chloride in tetrahydrofuran (5 ml). mixture was heated for 3 hours at reflux and overnight at room temperature. It was then diluted with ethyl acetate, washed with 1N hydrochloric acid, water (2 x) and brine, dried over magnesium sulfate and concentrated. The product was purified by flashchromatography (3% methanol in dichloromethane) and obtained as an oil. 25

¹H NMR (CDCl₃, 300 MHz) delta 1.90 (s, 3H), 2.36 (s, 3H), 2.92 (dd, J = 8Hz, 14Hz, 1H), 3.14 (dd, J =8Hz, 14Hz, 1H), 3.38 (t, J = 8Hz, 1H), 3.99 (s, 3H), 6.33 (s, 1H), 6.80 (dd, J = 2Hz, 8Hz, 1H), 7.09 (d, J =2Hz, 1H), 7.17 (dd, J = 2Hz, 8Hz, 1H), 7.38-7.60 (m, 6H), 7.94-7.98 (m, 4H), 9.00 (br s, 1H).

By the same method the following compounds were prepared: 3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(methylthio)-N-(phenylcarbonyl)propanamide (mp 62°C).

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3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-(methylthio)-N-(4-chlorophenylsulfonyl)-propanamide (mp 94-95°C).

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-(methylthio)-N-(4-fluorophenylsulfonyl)-propanamide (mp 60-62°C).

3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-(methylthio)-N-(methanesulfonyl)propanamide (mp 63-64°C).

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-(methylthio)-N-[(E)-2-phenylethenyl-sulfonyl)propanamide (oil).

1 H NMR (CDC1₃, 300 MHz) delta 2.05 (s, 3H), 2.34
15 (s, 3H), 3.02 (dd, J = 8Hz, 14Hz, 1H), 3.25 (dd, J =
8Hz, 14Hz, 1H), 3.48 (t, J = 8Hz, 1H), 3.98 (s, 2H),
6.30 (s, 1H), 6.95 (d, J = 14Hz, 1H), 6.96 (dd, J =
2Hz, 8Hz, 1H), 7.22 (d, J = 2Hz, 1H), 7.35-7.48 (m,
9H), 7.69 (d, J = 14Hz, 1H), 7.95-8.0 (m, 2H), 9.20 (br
s, 1H).

3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-(methylthio)-N-(2-naphthylsulfonyl)-propanamide (mp 163-166°C).

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzo-furan-5-yl]-2-(methylthio)-N-(N,N-diethylamino-sulfonyl)propanamide (oil).

 $1_{\rm H~NMR}$ (CDCl₃, 300 MHz) delta 1.12 (t, J = 7Hz, 6H), 2.08 (s, 3H), 2.36 (s, 3H), 2.96 (dd, J = 8Hz, 14Hz, 1H), 3.30 (q, J = 7Hz, 4H), 3.40 (t, J = 8Hz, 1H), 4.00 (s, 2H), 6.41 (s, 1H), 7.01 (dd, J = 2Hz, 8Hz, 1H), 7.26 (dd, J = 2Hz, 1H), 7.30 (d, J = 8Hz, 1H), 7.38-7.42 (m, 3H), 7.92-7.96 (m, 2H), 8.72 (s, 1H).

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EXAMPLE 12

Optical Resolution of 3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(propylthio)-

propanoic Acid

To a slurry of title product of Example 5 (1.6 g, 3.8 mmol) in benzene (35 ml) was added oxalyl chloride (1.8 ml, 21 mmol). Gas was evolved and the slurry turned into a clear yellow solution within 10 minutes. After two hours the solvent was removed, the residue was dissolved in dioxane (25 ml) and added dropwise to a solution of (S)-(+)-2-phenylglycinol (0.52 g, 3.8 mmol) and triethylamine (0.53 ml) in dioxane (10 ml). After 2 hours, the solvent was removed, water was added to the residue and the mixture was acidified with 6N hydrochloric acid. The solid was collected, dried and recrystallized from ethyl acetate/hexanes then from ethyl acetate to give the less polar isomer (on silica thin-layer chromatography, hexane/ethyl acetate, 1:2) as a pale yellow solid (0.41 g). The combined mother liquors were concentrated and the products separated by flash-chromatography (hexane/ethyl acetate,1:1). of the less polar isomer was thus obtained (0.14 g) as well as the more polar isomer (0.39 g).

The less polar amide (0.54 g, 0.97 mmol) and p-toluenesulfonic acid (2.8 g, 15 mmol) were placed in water (20 ml) and isopropanol (20 ml) and heated to reflux for three days. The solution was cooled, diluted with water (75 ml) and extracted with ethyl acetate (2 x 75 ml). The combined extracts were washed with water (2 x 75 ml) and brine (75 ml), dried over sodium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 16:4:1), then recrystallized from

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ethyl acetate (15 ml)/hexane (5 ml). The mother liquor was concentrated to give a white solid (83 mg, $[alpha]_D = +8.8^{\circ}$, c = 1.08, CDCl₃). This material was subsequently found to be greater than 95% optically pure by conversion back to the amide under neutral conditions (EEDQ) and its NMR spectrum was identical to the one of the racemic material.

In the same manner the more polar amide (0.39 g, 0.71 mmol) was converted into the levorotatory acid (81 mg, [alpha]_D = -9.4°, c = 1.06, CDCl₃).

EXAMPLE 13

2-Methoxy-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]phenyl]propanoic Acid

A. 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]-benzeneacetaldehyde

To a slurry of methoxymethyltriphenylphosphonium chloride (11 g, 32 mmol) in tetrahydrofuran (120 ml), cooled to 0°C, was added dropwise a 2.5M solution of n-butyllithium in hexanes (9.8 ml, 25 mmol). solution was stirred at 0°C for 30 minutes then a solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (Takeda U.S. Patent 4,725,610) (5.0 g, 16 mmol) in tetrahydrofuran (70 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. It was then diluted with water and extracted with ethyl acetate (3 x). The combined extracts were washed with water (2 x) and brine, dried over sodium sulfate and concentrated. The product, a mixture of E and Z 4-[2-[4-(2-methoxyethenyl)phenoxy]ethyl]-5-methyl-2-phenyloxazole, was isolated by flashchromatography (hexanes/ethyl acetate, 2:1) as a yellow solid (2.6 g).

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This solid (2.0 g, 6.0 mmol) was dissolved in tetrahydrofuran (100 ml) and 35% perchloric acid (10 ml) was added. The solution was heated to reflux for 1 hour then stirred overnight at room temperature, then diluted with water and extracted with ethyl acetate (2 x). The combined extracts were washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified by flash-chromatography (hexane/ethyl acetate, 4:1) and a yellow solid (0.51 g) was obtained.

Ethyl alpha-hydroxy-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate

To a solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzeneacetaldehyde (0.51 g, 1.6 mmol) and trimethylsylyl cyanide (0.21 ml, 1.6 mmol) in deuterochloroform (1 ml) was added zinc iodide (1 crystal). The solution was stirred overnight at room temperature, then concentrated to yield the product, 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-alpha-(trimethylsilyloxy)benzenepropanenitrile as an oil.

This oil was dissolved in hydrogen chloride (50 ml), the solution was cooled to 0°C, saturated with hydrogen chloride, and stirred overnight at room temperature, then saturated with hydrogen chloride again and stirred another 24 hours at room temperature. The mixture was poured into water, ethyl acetate was added, then 1N sodium hydroxide so as to get the product in solution. The organic layer was separated, washed with water and brine, dried over sodium sulfate and concentrated to a brown oil which was purified by flash-chromatography (hexanes/ethyl acetate, 3:2). The pure product was obtained as an oil (0.19 g).

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C. 2-Methoxy-4-3-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy)phenylpropanoic acid

A 60% sodium hydride dispersion (40 mg) was washed with hexane and suspended in tetrahydrofuran (10 ml). A solution of ethyl alpha-hydroxy-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzenepropanoate (0.19 g, 0.48 mmol) in tetrahydrofuran (2 ml) was added and after 10 minutes methyl iodide (0.3 ml, 4.8 mmol) was added. The mixture was stirred at room temperature overnight, then diluted with water, acidified with 2N hydrochloric acid and extracted with ethyl acetate (2 x). The combined extracts were washed with water and brine, dried over sodium sulfate and concentrated. The product was purified by flash-chromatography (hexanes/ethyl acetate/acetic acid, 10:10:1) and obtained as a yellow sticky solid.

 $1_{\rm H~NMR}$ (CDCl₃, 300 MHz) delta 2.36 (s, 3H), 2.96 (m, 3H), 3.05 (dd, J = 6Hz, 14Hz, 1H), 3.37 (s, 3H), 3.93 (dd, J = 6Hz, 9Hz, 1H), 4.17 (t, J = 9Hz, 2H), 6.79 (d, J = 8Hz, 1H), 7.10 (d, J = 8Hz, 1H), 7.36-7.40 (m, 3H), 7.92-7.96 (m, 2H).

EXAMPLE 14

2-Methoxy-3[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanoic Acid

A. 4-Benzoylamino-1-hexyn-5-one

Acetic anhydride (150 ml) was added to a solution of 2-benzoylamino-4-pentynoic acid (J. Org. Chem. 1983, 48, 3318) (73 g, 0.34 mol) in pyridine (200 ml) and the solution was heated to 90°C for 1 hour, then allowed to cool to 60°C and water (150 ml) was added. The mixture was heated to 85-90°C for 20 minutes, then cooled, diluted with water (300 ml) and extracted with chloroform (2 x 400 ml). The combined extracts were

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washed with water, 1N hydrochloric acid (3 x 500 ml), sodium bicarbonate and brine, and dried over magnesium sulfate. The chloroform solution was decolorized with charcoal, filtered and concentrated. The residue was recrystallized from butyl chloride to yield a tan solid (51 g, mp 101-103°C).

B. 5-Methyl-2-phenyl-4-(2-propynyl)oxazole

A solution of 4-benzoylamino-1-hexyn-5-one (30 g, 0.14 mol) in trifluoroacetic anhydride (100 ml) and trifluoroacetic acid (200 ml) was heated to 35-40°C for 6 hours. The solution was concentrated and the residue taken up in ethyl acetate (400 ml). To this solution was added saturated sodium bicarbonate solution (400 ml) followed by solid sodium bicarbonate until the water layer became neutral. The layers were separated, the organic layer was washed with brine, dried over magnesium sulfate and concentrated to give a brown oil (28 g) which was used as such.

20 C. 2-(5-Methyl-2-phenyl-4-oxazolyl)methyl-5-benzofurancarboxaldehyde

To a slurry of cuprous oxide (12 g, 84 mmol) in pyridine (150 ml) were added a solution of 5-methyl-2-phenyl-4-(2-propynyl) oxazole in pyridine (150 ml) followed by a solution of 4-hydroxy-3-iodobenzaldehyde (35 g, 0.14 mol) in pyridine (100 ml). Bis(triphenyl-phosphine)palladium (II) chloride (0.50 g, 0.7 mmol) was then added as a solid and the mixture was heated to reflux overnight. The mixture was cooled and concentrated. The residue was taken up in ethyl acetate (250 ml + 3 x 50 ml). The ethyl acetate solution was concentrated and the residue was extracted with hot cyclohexane. The hot solution was filtered and cooled and the solid was collected (29 g).

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D. 5-(2-Methoxyethenyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran

To a slurry of methoxymethylphosphonium chloride (34 g, 0.10 mol) and diisopropylamine (9.9 ml, 75 mmol) in tetrahydrofuran (500 ml) was added a 2.5M n-butyl-lithium solution in hexanes (30 ml, 75 mmol), at -10°C. After 1 hour at 10°C a solution of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofurancarboxaldehyde (16 g, 50 mmol) in tetrahydrofuran (200 ml) was added. The mixture was allowed to warm to room temperature over 2 hours, then poured into water (600 ml) and extracted with ether (3 x). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was isolated by flash-chromatography (hexanes/ethyl acetate, 4:1) as a solid (14 g).

E. 5-(2,2-Dimethoxyethyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran

A solution of 5-(2-methoxyethenyl)-2-(5-methyl-2-phenyl-4-oxazolyl)methylbenzofuran (0.69 g, 2.0 mmol) and p-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) in methanol (30 ml) was heated to reflux overnight. The solvent was removed, the residue was taken up in ethyl acetate, the solution was washed with 5% sodium bicarbonate and brine, dried over magnesium sulfate and concentrated to an oil which slowly solidified on standing (0.75 g).

F. 2-Methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl)propanenitrile

To a solution of 5-(2,2-dimethoxyethyl)-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran (0.75 g, 2.0 mmol) in dichloromethane (15 ml) were added trimethylsilyl cyanide (0.80 ml, 6.0 mmol) and boron trifluoride etherate (50 µl, 0.5 mmol). After 1 hour

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the solution was diluted with dichloromethane, washed with 5% sodium bicarbonate, water and brine, dried over magnesium sulfate and concentrated. The product was purified by flash-chromatography (hexanes/ethyl acetate, 2:1) and isolated as a solid (0.64 g, mp 107-109°C).

G. 2-Methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanoic acid

A mixture of 2-methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanenitrile (0.64 g, 1.7 mmol), ethanol (30 ml) and 6N sodium hydroxide (10 ml) was heated to reflux for 3 hours. Water (30 ml) was added and the solution was acidified with concentrated hydrochloric acid (6 ml), then extracted with ethyl acetate (2 x). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. The product was recrystallized from ethyl acetate/hexanes and obtained as a white solid (0.47 g, mp 159-160.5°C).

Using the corresponding alcohols, the following compounds were prepared by the same procedure:

2-Ethoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanoic acid (mp 164-165.5°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-propoxypropanoic acid (mp 139.5-140.5°C)

3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(2-propenyloxy)propanoic acid (mp 154-155.5°C)

3-[2-((5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(phenylmethoxy)propanoic acid (mp 123-126°C)

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2-(3-Hydroxypropoxy)-3-[2-((5-methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]propanoic acid (mp 125-127°C)

3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)benzofuran-5-yl]-2-(2-propynyloxy)propanoic acid (mp 148-150°C)

From (2H)-3,4-dihydro-2-[(4-(phenylmethoxy)-phenyl)methyl]-6-benzopyrancarboxaldehyde (U.S. Patent 4,798,835), sodium (2H)-3,4-dihydro-alpha-ethoxy-2-(4-phenylmethoxy)phenylmethyl-6-benzopyranpropanoate was prepared by the same sequence. Mp 61-64°C

EXAMPLE 15

2-Methoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanamide

A solution of the Step F intermediate, Example 14 (0.24 g, 0.64 mmol) in ethanol (20 ml) was saturated with hydrogen chloride and stirred at room temperature for three days. The solvent was removed, water was added followed by saturated sodium bicarbonate to bring the pH to neutral. This mixture was extracted with ethyl acetate (2 x), the combined extracts were washed with brine and dried over magnesium sulfate overnight. The product was isolated by flash-chromatography (hexanes/ethyl acetate, 1:1) as a white solid (58 mg, mp 164-167°C).

2-Ethoxy-3-[2-((5-methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]propanamide was obtained by the same method. Mp 165-168°C.

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EXAMPLE 16

- (E) and (Z)-3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-methyl)benzofuran-5-yl]-2-methoxy-2-propenamide
- (E) and (Z)-3-[2-((5-Methyl-2-phenyl-4-oxazolyl)-Α. 5 methyl) benzofuran-5-yl]-2-methoxy-2-propenenitrile To a slurry of 60% sodium hydride (88 mg, 2.2 mmol) in dimethylformamide (15 ml) was added at 45°C methoxyacetonitrile (0.21 g, 3.0 mmol). This solution was allowed to cool and after 30 minutes was slowly 10 added to a warm (50°C) solution of 2-(5-methyl-2phenyl-4-oxazolyl)methyl-5-benzofuran carboxaldehyde (Example 14) (0.63 g, 2.0 mmol) in dimethylformamide The mixture was heated to 75-80°C for 1 hour then cooled and poured into a water/ethyl acetate 15 The layers were separated, the aqueous layer was extracted with ethyl acetate, the combined organic phases were washed with water (3 x), dried over magnesium sulfate and concentrated. Flashchromatography (hexanes/ethyl acetate, 2.5:1) afforded 20 the two geometrical isomers of the product, the less polar isomer (assigned as Z) as a solid (0.10 g), and the more polar isomer (E) as an oil (0.15 g).
 - B. (Z)-3-[2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-methoxy-2-propenamide

A solution of (2)-3-[2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-methoxy-2-propenenitrile (0.10 g, 0.27 mmol) in methanol (10 ml) and sodium hydroxide (2 ml) was heated to reflux for 3 hours then cooled, acidified with 6N hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was purified by

flash chromatography (ethyl acetate/methanol/acetic acid, T:1:1) and obtained as a solid (31 mg, m.p. 166-169°C).

The (E) isomer was subjected to the same hydrolysis conditions, and the product isolated as a solid (26 mg, 5 m.p. 160-164°C).

EXAMPLE 17

(E)-3-[2-(5-Methyl-2-phenyl-4-oxazolyl)
methyl-5-benzofuranyl]-2-phenoxy-2-propenamide

- (E) -3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl-5benzofuranyl]-2-phenoxy-2-propenenitrile. To a slurry of 10 60% sodium hydride (0.10 g, 2.5 mmol) in dimethylformamide (15 ml) was added at 60°C phenoxyacetonitrile (0.21 g, 3.0 mmol). This solution was kept at 60°C for 40 minutes, cooled to room temperature and was slowly added to a warm (80°C) solution of 2-(5-methyl-2-phenyl-4-oxazolyl)methyl-15 5-benzofurancarboxaldehyde (0.40 g, 2.5 mmol) in dimethylformamide (20 ml). The mixture was heated to 75-80°C for 15 minutes, then cooled and poured into a solution of water (50 ml) and 1N HCl (2.5 ml). mixture was extracted with ethyl acetate (2X). 20 combined organic phases were washed with water (3X) and brine, dried over magnesium sulfate and concentrated. Flash chromatography (hexanes/ethyl acetate/triethylamine, 50:50:1) afforded the product as an oil (0.19 g).
- B. (E)-3-[2-(5-Methyl-2-phenyl-4-oxazolyl)methyl)-5-benzofuranyl]-2-phenoxy-2-propenamide. A solution of (E)-3-[2-(5-methyl-2-phenyl-4-oxazolyl)methyl-5-benzofuranyl]-2-phenoxy-2-propenenitrile (0.19 g, 0.44 mmol) in ethanol (10 ml) and sodium hydroxide (2 ml) was heated to reflux for 24 hours, then cooled, poured into a

mixture of water (50 ml) and ethyl acetate and acidified with 6N hydrochloric acid. The layers were separated, the aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 48:8:1) followed by recrystallization from ethyl acetate/hexanes (30 mg, m.p. 171-172.5°C).

EXAMPLE 18

10 Sodium 2-benzyloxy-3-[2-(4-benzyloxybenzyl)3,4-dihydro-2H-benzopyran-6-yl]propanoate

2-(4-Benzyloxybenzyl)-3,4-dihydro-6-(2-methoxyethenyl)-2H-benzopyran. To a slurry of methoxymethylphosphonium chloride (12.5 g, 37 mmol) and diisopropylamine 15 (9.9 ml, 27.5 mmol) in tetrahydrofuran (40 ml) was added a 2.5 M n-butyllithium solution in hexanes (5.5 ml, 27.5 mmol) at -10°C. After 1 hour at -10°C a slurry of 2-(4benzyloxy)benzyl-3,4-dihydro-6-formyl-2H-benzopyran (U.S. patent no. 4,798,835) (4.9 g, 18 mmol) in tetrahydrofuran (100 ml) was added. The mixture was allowed to warm to 20 room temperature over 2 hours, then was poured into water (200 ml) and extracted with ethyl acetate (3X). combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 25 4:1) as an oil (2.1 g).

B. 2-(4-Benzyloxybenzyl)-6-[2,2-bis(benzyloxy) ethyl]-3,4-dihydro-2H-benzopyran. A solution of 2-[(4-benzyloxy)benzyl]-3,4-dihydro-6-(2-methoxyethenyl)-2H-benzopyran (0.29 g, 0.75 mmol) and benzyl alcohol (1.0 ml, 9.7 mmol) containing Amberlyst 15° ion-exchange resin (100

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mg) was heated to reflux overnight. The resin was filtered and washed with chloroform, the chloroform and the bulk of the benzyl alcohol were removed in vacuo and the residue was purified by flash chromatography

5 (hexanes/ethyl acetate, 4:1) to give the pure product as an oil (0.40 g).

- C. 2-Benzyloxy-3-[2-(4-benzyloxybenzyl)-3,4-dihydro-2H-benzopyran-6-yl]propanenitrile. To a mixture of 2-[(4-benzyloxy)benzyl]-6-[2,2-bis(benzyloxy)ethyl]-3,4-dihydro-2H-benzopyran (0.40 g, 0.70 mmol) and trimethylsilyl cyanide (2 ml) was added boron trifluoride etherate (2.0 6ml, 0.2 mmol). After 1 hour the reaction was quenched with saturated sodium bicarbonate and the solution was extracted with ethyl acetate (2X). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 2:1) and isolated as an oily solid (0.23 g).
- D. Sodium 2-benzyloxy-3-[-2-(4-benzyloxybenzyl)-3,4
 dihydro-2H-benzopyran-6-yl]propanoate. A mixture of 2benzyloxy-3-[2-(4-benzyloxybenzyl)-3,4-dihydro-2Hbenzopyran-6-yl]propanenitrile (0.23 g, 0.47 mmol),
 ethanol (10 ml) and 6N sodium hydroxide (2 ml) was heated
 to reflux for 5 hours. Water (50 ml) was added and the

 solution was acidified with concentrated hydrochloric acid
 (2 ml), then extracted with ethyl acetate (2X). The
 combined organic layers were washed with brine, dried over
 magnesium sulfate and concentrated to an oil (0.19 g).
 The product was dissolved in methanol and treated with
 sodium methoxide (21 mg). The solvent was removed and the
 solid dried (7 mg, m.p. 165-169°C).

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EXAMPLE 19

(S) -2-Ethoxy-3-{2-[5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran-5-yl}propanoic acid

A. (S)-4-Benzyl-3-(ethoxyacetyl) oxazolidin-2-one.
5 To a solution of (S)-4-benzyloxazolidin-2-one (4.4 g, 25 mmol) in dry tetrahydrofuran (20 ml), cooled to -78°C, was added n-butyllithium (2.5M solution in hexane, 10 ml, 25 mmol) dropwise. Another 20 ml of tetrahydrofuran was added to facilitate stirring. A solution of ethoxyacetyl
10 chloride (3.0 g, 25 mmol) in tetrahydrofuran (5 ml) was added and the mixture was stirred at -78°C for 30 minutes, then warmed to room temperature, poured into water and extracted with ethyl acetate (3X). The combined extracts were washed with water and brine, dried over sodium
15 sulfate and concentrated to a yellow oil (4.3 g, [α]_D = +56.7°).

5-{(1R, 2S)-1-hydroxy-2-ethoxy-3-[(S)-4-benzyl-2oxo-3-oxazolidinyl]-3-oxopropyl}-2-[(5-methyl-2-phenyl-4oxazolyl)methyl]benzofuran. To a solution of (S)-4-20 benzyl-3-(ethoxyacetyl)oxazolidin-2-one (1.0 g, 3.8 mmol) in dichloromethane (10 ml), cooled to 0°C, was added freshly distilled dibutylboron triflate (1.1 ml, 4.6 mmol) dropwise, followed by triethylamine (0.69 ml, 4.9 mmol). After 5 minutes the solution was cooled to -78°C and a 25 precooled solution of 2-(5-methyl-2-phenyl-4-oxazolyl) methyl-5-benzofurancarboxaldehyde (1.33 g, 4.2 mmol) in dichloromethane (5 ml) was added. After 20 minutes the mixture was warmed to 0°C and stirred at that temperature for 1 hour then quenched with a solution of pH 7 buffer 30 (10 ml) in methanol (30 ml), followed by a solution of 30% hydrogen peroxide (10 ml) in methanol (30 ml), and stirred at 0°C for 1 hour. The mixture was then diluted with

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water and extracted with ethyl acetate (3X). The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 1:1) and obtained as a yellow solid (1.16 g, m.p. 66°C).

- c. 5-{(S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3oxazolidinyl]-3-oxopropyl}-2-[(5-methyl-2-phenyl-4oxazolyl)methyl]benzofuran. To a solution of 5-{(1R,
 2S)-1-hydroxy-2-ethoxy-3-[(S)-4-benzyl-2-oxo-3oxazolidinyl]-3-oxopropyl}-2-[(5-methyl-2-phenyl-4oxazolyl)methyl]benzopyran (1.0 g, 1.72 mmol) in
 trifluoroacetic acid (20 ml) was added triethylsilane (3.0
 ml, 19 mmol). The solution was stirred for 4 days at room
 temperature then diluted with ethyl acetate, washed with
 water and saturated sodium bicarbonate solution (3X),
 dried over sodium sulfate and concentrated. The product
 was isolated by flash chromatography (hexanes/ethyl
 acetate, 5:1) as a pale yellow solid (0.44 g).
- D. (S)-2-Ethoxy-3-{2-[(5-methyl-2-phenyl-4-oxazolyl)
 20 methyl]benzofuran-5-yl}propanoic acid. 5-{(S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl}-2-[(5-methyl-2-phenyl-4-oxazolyl)methyl]benzofuran (0.15 g, 0.26 mmol) was dissolved in tetrahydrofuran (5 ml). The solution was cooled to 0°C and 0.5N lithium hydroxide (1.1 ml, 0.52 mmol) was added. After 15 minutes the bulk of the ethanol was removed, the residue was acidified with 1N HCl, diluted with water and extracted with ethyl acetate (3X). The combined extracts were washed with brine, dried over sodium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate/acetic acid, 10:10:1) then recrystallized from hexanes/ethyl acetate and obtained as a white solid (48 mg, m.p. 129°C, [α]_D = -12.5° (c 0.99, CDCl₃)).

Using the appropriate reagents, the following compounds were prepared by the same procedure.

- (R)-2-Ethoxy-3-{2-[(5-methyl-2-phenyl-4-oxazolyl) methyl]benzofuran-5-yl}propanoic acid (m.p. 129°C, $[\alpha]_D = +9.3$ ° (c 0.65, CDCl₃)).
 - (R)-3-{2-[(5-Methyl-2-phenyl-4-oxazolyl)methyl]benzo-furan-5-yl}-2-phenoxypropanoic acid (m.p. 174-175°C, $[\alpha]_D = -13.1^\circ$ (c 0.50, CDCl₃)).
- (S)-3-{2-[(5-Methyl-2-phenyl-4-oxazolyl)methyl]benzo-10 furan-5-yl}-2-phenoxypropanoic acid (m.p. 165°C, $[\alpha]_D$ = +8.1° (c 0.07, CDCl₃)).

EXAMPLE 20

3-{[4-(4-Benzyloxyphenyl)ethoxy] phenyl}-2-methoxypropanoic acid

- 15 A. 1-Benzyloxy-4-(2-hydroxyethyl) benzene. To a solution of 4-hydroxyphenethyl alcohol (33 g, 0.24 mol) in dry dimethylformamide (200 ml), cooled to 0°C, was added potassium tert-butoxide (29 g, 0.26 mol) by portions. After 10 minutes, benzyl bromide (41 g, 0.28 mol) was 20 added slowly. The reaction mixture was stirred for 15 minutes at 0°C, then for 3 hours at room temperature and was quenched with water (200 ml). The precipitate was collected, dried and recrystallized from isopropyl ether/hexanes (34 g).
- B. 4-[(4-Benzyloxyphenyl)ethoxy]benzonitrile. To a suspension of sodium hydride (60%, 2.2 g, 55 mmol) in dry tetrahydrofuran (250 ml) was added a solution of 1-benzyloxy-4-(2-hydroxyethyl)benzene (11.4 g, 50 mmol) in

tetrahydrofuran (50 ml). The reaction was heated to 40°C for 1 hour. 4-Fluorobenzonitrile (6.7 g, 55 mmol) was added and the mixture was heated to reflux for 5 hours, cooled and neutralized with concentrated HCl. The precipitate was filtered, the filtrate was concentrated to dryness and the resulting solid was recrystallized from ethanol (12 g).

- C. 4-[(4-Benzyloxyphenyl)ethoxy]benzaldehyde. 4[(4-Benzyloxyphenyl)ethoxy]benzonitrile (4.9 g, 15 mmol)
 was dissolved in toluene (300 ml) and treated with a 1.5M
 toluene solution of diisobutylaluminum hydride (10 ml, 15
 mmol). The reaction mixture was stirred overnight then
 quenched with a saturated sodium potassium tartrate
 solution (100 ml). The organic layer was washed with 5%
 sulfuric acid (50 ml), saturated sodium bicarbonate (100
 ml) and brine, dried over magnesium sulfate and
 concentrated to dryness. The product was purified by
 flash chromatography (hexanes/ethyl acetate, 5:1) and
 obtained as an oil (4.0 g).
- This aldehyde was converted into 2-methoxy-3-{[4-(4-benzyloxyphenyl)ethoxy]phenyl}propanoic acid (m.p. 65-69°C) by the sequence described in Example 18.

Using the appropriate reagents, the following compounds were prepared by the same procedure.

- 3-{[4-(4-Benzyloxyphenyl)ethoxy]phenyl}-2-ethoxy-propanoic acid (m.p. 62-63.5°C).
 - 3-{[4-(4-(3-Fluorobenzyloxy)phenyl)ethoxy]phenyl}-2-methoxypropanoic acid (m.p. 58-62°C).
- 2-Ethoxy-3-{[4-(4-(3-fluorobenzyloxy)phenyl)ethoxy]
 30 phenyl}propanoic acid (m.p. 54.5-57.5°C).

2-Benzyloxy-3-{[4-(4-benzyloxyphenyl)ethoxy]phenyl) propanoic acid (m.p. 85-86°C).

3-[3-(5-Ethyl-2-pyridyl)propoxy]phenyl-2-methoxy-propanoic acid (m.p. 81-82°C).

5 2-Ethoxy-3-[3-(5-ethyl-2-pyridyl)propoxy]phenyl-propanoic acid (m.p. 80-81°C).

3-[3-(5-Ethyl-2-pyridyl)propoxy]phenyl-2-propoxy-propanoic acid (m.p. 89-90°C).

2-Ethoxy-3-{4-[3-(5-methyl-2-phenyl-4-oxazolyl) propanoyl]phenyl}propanoic acid (oil). ¹H NMR (250 MHz, CDCl₃) δ 1,11 (t, J=6.9 Hz, 3H), 2.37 (s, 3H), 2.92 (t, J=7.1 Hz, 2H), 2.94-3.09 (m, 2H), 3.13 (dd, J=13.9 Hz, 4.04 Hz, 1H), 3.35 (t, J=7.1 Hz, 3H), 3.60 (m, 1H), 3.61 (dd, J=9.1 Hz, 7.0 Hz, 1H), 7.32 (d, J=8.3 Hz, 2H), 7.36-7.44 (m, 3H), 7.89 (d, J=8.3 Hz, 2H), 7.94-7.98 (m, 2H), 8.95 (br s, 1H).

EXAMPLE 21

3-[2-(4-Benzyloxybenzyl)benzofuran-5-yl]-2-ethoxypropanoic acid

A. 5-Bromo-2-(4-benzyloxybenzoyl)benzofuran. 5-Bromosalicylaldehyde (2.9 g, 14.5 mmol), cesium carbonate (2.5 g, 7.7 mmol) and acetonitrile (40 ml) were combined and heated to reflux for 30 minutes. The mixture was cooled to 0°C and a solution of 4'-benzyloxy-2-bromoaceto-phenone (J. Het. Chem., 2, 310 (1965)) (4.7 g, 15 mmol) in acetonitrile (20 ml) was added. The cooling bath was removed, the mixture stirred at room temperature for 2.5 hours and the precipitate collected (4.5 g).

- B. 5-Bromo-2-(4-benzyloxybenzyl)benzofuran. 5Bromo-2-(4-benzyloxybenzoyl)benzofuran (9.0 g, 22 mmol),
 sodium cyanoborohydride (10.4 g, 0.17 mol), zinc iodide
 (10.5 g, 0.35 mol) and 1,2-dichloroethane (350 ml) were
 combined and heated to reflux for 6 hours. The mixture
 was cooled, quenched with saturated ammonium chloride (500
 ml), acidified with concentrated HCl and stirred for 30
 minutes. The layers were separated, the aqueous layer was
 extracted with dichloromethane (400 ml) and the combined
 organic layers were washed with water and brine, dried
 over magnesium sulfate and concentrated, leaving a white
 solid (8.5 g).
- C. 2-(4-Benzyloxybenzyl)-5-cyanobenzofuran. mixture of 5-bromo-2-(4-benzyloxybenzyl)benzofuran (4.4 g, 11 mmol), copper cyanide (1.50 g, 17 mmol) and bis(tri-15 phenylphosphine) palladium (II) chloride (0.79 g, 1.1 mmol) in DMF (40 ml) was heated to reflux overnight. The mixture was cooled, ethyl acetate (200 ml) and concentrated ammonium hydroxide (100 ml) were added. organic layer was washed with water (3X) and brine, dried 20 over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 5:1) and obtained as a solid (2.6 g, m.p. 131.5-132.5°C). This compound was transformed into the corresponding aldehyde as in Example 20 and into 3-[2-(4-benzyloxy-25 benzyl)benzofuran-5-yl]-2-ethoxypropanoic acid (m.p. 91-94°C) by the sequence described in Example 18.

The following compounds were prepared by the same sequence from the appropriate starting materials and reagents.

3-[2-(4-B@nzyloxybenzyl)benzofuran-5-yl]-2-methoxy-propanoic acid (m.p. 98-100°C).

2-Benzyloxy-3-[2-(4-benzyloxybenzyl)benzofuran-5-yl] propanoic acid (m.p. 115-116.5°C).

EXAMPLE 22

(S)-3,4-Dihydro-2-ethoxy-3-{(R)-2-[4-(3-fluorobenzyloxy) benzyl]-2H-benzopyran-6-yl}propanoic acid 5

(R)-(-)-3, 4-Dihydro-2-(4-methoxybenzyl)-2Hbenzopyran. (R)-(-)-3,4-Dihydro-2-trifluoromethanesulfonyloxymethyl-2H-benzopyran (23.0 g, 78 mmol) and copper (I) bromide dimethyl sulfide complex (2.8 g, 13 mmol) were dissolved in tetrahydrofuran (400 ml) under a 10 nitrogen atmosphere and cooled to -10°C. 4-Anisylmagnesium bromide (215 ml of a 1M solution in tetrahydrofuran, 0.215 mol) was added dropwise over 30 minutes, keeping the temperature below -5°C. The solution was stirred for 3 hours at 0°C and then slowly poured into a mixture of water (800 ml) containing ammonium chloride (96 g, 1.8 mol) and methylene chloride (400 ml). The layers were separated and the aqueous portion was extracted with methylene chloride (400 ml). The combined organics were washed with 10% ammonium chloride (2 X 400 ml), water (250 ml), and brine (250 ml). The methylene chloride layer was dried (MgSO4), filtered and concentrated in vacuo. residue was purified on silica gel using hexanes/methylene chloride (1:1) as eluent to afford 18.5 g (92% yield) of 25 the title product as an oil. $[\alpha]_D$ -99.2° (c 1.7, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.6-1.7 (m, 1H), 1.9-2.0 (m, 1H), 2.7-2.8 (m, 3H), 3.1 (dd, 1H), 3.8 (s, 3H), 4.1 (m, 1H), 6.8 (m, 3H), 7.0 (m, 2H), 7.2 (m, 2H).

(R) - (-) -3, 4-Dihydro-2-(4-hydroxybenzyl) -2H-benzo-(R)-(-)-3,4-Dihydro-2-(4-methoxybenzyl)-2H-benzo-30 pyran. pyran (812 mg, 3.2 mmol), and lithium iodide (750 mg, 5.6 mmol) were dissolved in 2,4,6-collidine (2 ml) and heated

to reflux for 24 hours. The reaction mixture was cooled, diluted with ethyl acetate (20 ml) and 10% HCl (20 ml), and stirred for 10 minutes. The layers were separated and the aqueous portion was extracted with ethyl acetate (50 ml). The combined organics were washed with water (20 ml), brine (20 ml), and were dried (MgSO₄). The solvent was removed in vacuo and the residue purified on silica gel using hexanes/ethyl acetate (3:1) as eluent to afford 730 mg of a colorless oil which crystallized upon standing, m.p. 60-62°C; [a]_D -110.2° (c 1.0, MeOH); ¹H NMR (300 MHz, CDCl₃) & 1.7 (m, 1H), 2.0 (m, 1H), 2.7-2.8 (m, 3H), 3.1 (dd, 1H), 4.2 (m, 1H), 6.8 (m, 3H), 7.0-7.2 (m, 4H).

- C. (R)-(-)-2-(4-Acetoxybenzyl)-3,4-dihydro-2Hbenzopyran. (R)-(-)-3,4-Dihydro-2-(4-hydroxybenzyl)-2H-15 benzopyran (5.0 g, 20 mmol), 4-dimethylaminopyridine (240 mg, 2 mmol), triethylamine (2.6 g, 25 mmol) and acetic anhydride (2.9 g, 28 mmol) were dissolved in methylene chloride (75 ml) and stirred at room temperature for 2 hours under a nitrogen atmosphere. The solvent was 20 removed in vacuo and the residue purified on silica gel using hexanes/ethyl acetate (3:1) as eluent to afford an oil which was crystallized from hexanes to yield 4.0 g of the title product, m.p. 64-65°C; $[\alpha]_D$ -98.9° (c 1.3, MeOH); 1 H NMR (300 MHz, CDCl₃) δ 1.7 (m, 1H), 1.9 (m, 1H), 2.3 (s, 3H), 2.7 (m, 2H), 2.8 (dd, 1H), 3.1 (m, 1H), 4.2 (m, 1H), 6.8 (m, 2H), 7.0 (m, 3H), 7.2 (m, 2H).
- D. (R)-(-)-2-(4-Acetoxybenzyl)-3,4-dihydro-6formyl-2H-benzopyran. (R)-(-)-2-(4-Acetoxybenzyl)-3,4dihydro-2H-benzopyran (16.6 g, 59 mmol), N-methylformanilide (23.9 g, 0.177 mol), and phosphorus oxychloride
 (18.0 g, 0.118 mol) were heated to 90°C for 3 hours under
 a nitrogen atmosphere. The reaction mixture was cooled
 and poured into ice water (250 ml). The aqueous solution
 35 was extracted with ethyl acetate (2 X 500 ml) and the

combined organics were washed with saturated NaHCO₃ (250 ml), water (250 ml), brine (250 ml), and dried (MgSO₄). The solvent was removed <u>in vacuo</u> and the residue purified on silica gel using hexanes/ethyl acetate (3:1) as eluent to afford 15.7 g (86% yield) of the 6-formyl derivative, ¹H NMR (300 MHz CDCl₃) δ 1.8 (m, 1H), 2.1 (m, 1H), 2.3 (s, 3H), 2.8 (m, 2H), 2.9 (m, 1H), 3.1 (m, 1H), 4.3 (m, 1H), 6.9 (d, 1H), 7.0 (d, 2H), 7.3 (d, 2H), 7.6 (m, 2H), 9.8 (s, 1H).

- 10 (R)-(-)-3,4-Dihydro-6-formyl-2-(4-hydroxybenzyl)-2H-benzopyran. (R)-(-)-2-(4-Acetoxybenzyl)-3,4-dihydro-6formyl-2H-benzopyran (15.7 g, 51 mmol) was dissolved in a mixture of methanol (200 ml), tetrahydrofuran (200 ml) and 2M NaOH (200 ml) and stirred at room temperature for 2 15 The reaction mixture was concentrated in vacuo, diluted with water (100 ml) and acidified with 10% HCl (250 ml). The aqueous solution was extracted with ethyl acetate (2 X 500 ml) and the combined organics were washed with water (250 ml), brine (250 ml), and dried (MgSO₄). 20 The solvent was removed in vacuo and the residue was crystallized from hexanes/ethyl acetate (3:1) to afford 10.1 g of the title compound, m.p. $134-135^{\circ}$ C; $\{\alpha\}_{p}$ -155.2° (c 1.0, MeOH); 1 H NMR (300 MHz CDCl₃) δ 1.6 (m, 1H), 1.9 (m, 1H), 2.8 (m, 3H), 3.0 (dd, 1H), 4.2 (m, 1H), 5.1 (br 25 s, 1H, OH), 6.7 (d, 2H), 6.8 (d, 1H), 7.0 (d, 2H), 7.5 (m, 2H), 9.7 (s, 1H).
- F. (R)-2-[4-(3-Fluorobenzyloxy)benzyl]-3,4-dihydro-6-formyl-2H-benzopyran. To a solution of (R)-3,4-dihydro-6-formyl-2-(4-hydroxybenzyl)-2H-benzopyran (1.8 g, 6.7 mmol) in DMF (10 ml) at 0°C was added potassium tert-butoxide (0.83 g, 7.4 mmol). After 30 minutes m-fluorobenzyl bromide (0.91 ml, 7.4 mmol) was added and the resulting slurry was warmed to room temperature and stirred for 2 hours. Water was added and the precipitate was collected, washed with water and air dried (2.5 g).

- $(R) -6 \{ (1R, 2S) -1 Hydroxy -2 ethoxy -3 [(S) -4 (S) -4 (S)$ benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl}-2-[4-(3fluorobenzyloxy) benzyl]-2H-benzopyran. Trifluoromethanesulfonic acid (0.64 ml, 7.2 mmol) was added to a 1M 5 solution of triethylborane in toluene (7.2 ml, 7.2 mmol) and the mixture was heated to 40°C for 1 hour then cooled to 0°C. A solution of (S)-4-benzyl-3-(ethoxyacetyl) oxazolidin-2-one (Example 19) (0.64 g, 3.6 mmol) in dichloromethane (5 ml) was added, followed by diisopropyl-10 ethylamine (1.33 ml, 7.6 mmol). After 30 minutes the solution was cooled to -78°C and a solution of (R)-2-[4-(3-fluorobenzyloxy)benzyl]-3,4-dihydro-6-formyl-2Hbenzopyran (1.0 g, 3.6 mmol) in dichloromethane (15 ml) was added. The mixture was stirred at -78°C for 2 hours 15 then 30 minutes at 0°C and quenched with pH 7 buffer (5 ml). The mixture was diluted with ether, the organic layer was washed with water and brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 20 3:2) as an oil (85 mg).
- H. (R)-6-{(S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl}-2-[4-(3-fluorobenzyloxy) benzyl]-2H-benzopyran. (R)-6-{(1R, 2S)-1-Hydroxy-2-ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-3-oxopropyl}-2-[4-(3-fluorobenzyloxy)benzyl]-2H-benzopyran (80 mg, 0.13 mmol) was dissolved in trifluoroacetic acid (2 ml) and triethylsilane (0.20 ml) was added. After 30 minutes the solution was diluted with ether, washed with water (2X) and saturated sodium bicarbonate (2X), dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl acetate, 2:1) and obtained as an oil (39 mg).
 - I. (S)-2-Ethoxy-3-{(2R)-2-[4-(3-fluorobenzyloxy)
 benzyl]-3,4-dihydro-2H-benzopyran-6-yl}propanoic acid.
 (R)-6-{(S)-2-Ethoxy-3-[(S)-4-benzyl-2-oxo-3-oxazolidinyl]-

3-oxopropy1}-2-[4-(3-fluorobenzyloxy)benzyl]-2H-benzopyran (39 mg, 63 mmol) was dissolved in tetrahydrofuran (1.5 ml) at 0°C and treated with 0.5N lithium hydroxide (1 ml). The reaction mixture was warmed to room temperature and stirred for 1 hour, then acidified with 1N hydrochloric acid and extracted with ethyl acetate (3X). The combined extracts were washed with water and brine, dried over magnesium sulfate and concentrated. The product was purified by flash chromatography (hexanes/ethyl 10 acetate/acetic acid, 15:5:1) and isolated as an oil (30 mg). ¹H NMR (300 MHz, CDCl₃) δ 1.16 (t, J=6.9 Hz, 3H), 1.67 (m, 1H), 1.93 (m, 1H), 2.68-2.72 (m, 2H), 2.79 (dd, J=13.8 Hz, 6.9 Hz, 1H), 2.88 (dd, J=14.4 Hz, 7.7 Hz, 1H), 3.00 (dd, J=12.2 Hz, 4.3 Hz, 1H), 3.05 (dd, J=13.4 Hz, 7.6 15 Hz, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 4.01 (dd, J=7.5 Hz, 4.2 Hz, 1H), 4.12 (m, 1H), 5.03 (s, 2H), 6.71 (d, J=8.2 Hz, 1H), 6.88-7.02 (m, 3H), 6.89 (d, J=8.5 Hz, 2H), 7.12-7.18 (m, 2H), 7.17 (d, J=8.6 Hz, 2H), 7.32 (m, 1H).

The following compounds were prepared from the 20 corresponding aldehydes (Example 20) by the same sequence.

- (S) Sodium 2-ethoxy-3-{[4-(4-(3-fluorobenzyloxy) phenyl)ethoxy]phenyl}propanoate (m.p. 195-200°C).
- (R) Sodium 2-ethoxy-3-{[4-(4-(3-fluorobenzyloxy) phenyl)ethoxy]phenyl}propanoate (m.p. 200-205°C).

25

EXAMPLE 23

Sodium 3,4-dihydro-2-ethoxy-3-[(R)-2-(4-benzyloxybenzyl)-2H-benzopyran-6-yl]propanoate

(R)-(-)-3,4-Dihydro-6-formyl-2-(4-hydroxybenzyl)-2H-benzopyran (Example 22) was transformed into the title

compound by a sequence analogous to the one described in Example 18, m.p. 160-170°C (dec.).

Using the corresponding reagent, 3,4-dihydro-2-ethoxy-3-{(R)-2-[4-(5-ethyl-2-pyridyl)methoxy]-2H-benzopyran-6-yl}propanoate was prepared by the same method, m.p. 108-109°C.

EXAMPLE 24

Sodium 3,4-dihydro-2-ethoxy-3-[(R)-2-benzyl-2H-benzopyran-6-yl]propanoate

(R)-(-)-3,4-Dihydro-6-formyl-2-benzyl-2H-benzopyran was prepared from (R)-(-)-3,4-dihydro-2-trifluoromethane-sulfonyloxymethyl-2H-benzopyran and phenylmagnesium bromide as described in Example 22 and converted to the title compound as in Example 18 (foam). ¹H NMR (300 MHz, CDCl₃) δ 1.2 (t, 3H), 1.7 (m, 1H), 2.0 (m, 1H), 2.8-3.1 (m, 6H), 3.4 (m, 1H), 3.6 (m, 1H), 4.0 (dd, 1H), 4.1 (m, 1H), 6.7 (d, 2H), 6.9 (s, 1H), 6.95 (dd, 1H), 7.2 (m, 5H).

EXAMPLE 25

2-Phenoxy-3-[4-(2-phenyl)ethoxyphenyl]propanoic acid

A. (S)-4-Benzyl-3-[(1S),(2R)-2-(4-benzyloxyphenyl)2-hydroxy-1-phenoxyethyl]-2-oxazolidinone. Trifluoromethanesulfonic acid (5.0 ml, 56 mmol) was added to a
solution of triethylborane in hexanes (56 ml of a 1M
solution, 56 mmol). After the bubbling stopped, the

25 solution was heated to 40°C for 1 hour then cooled to 0°C,
a solution of (S)-4-benzyl-3-(phenoxyacetyl)oxazolidin-2-

one (prepared as in Example 19) (5.0 g, 28 mmol) in dichloromethane (90 ml) was added followed by diisopropylethylamine (12.3 ml, 71 mmol) dropwise. After 30 minutes the solution was cooled to -78°C and treated with a solution of 4-benzyloxybenzaldehyde (6.0 g, 28 mmol) in dichloromethane (80 ml). After 2 hours at -78°C, the solution was warmed to 0°C, stirred for 30 minutes and quenched with pH 7 buffer. The layers were separated, the aqueous portion was extracted with dichloromethane, the combined extracts were washed with water and brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 1:1) as an oil (6.5 g).

- B. (S)-4-Benzyl-3-[(1S)-2-(4-benzyloxyphenyl)-115 phenoxyethyl]-2-oxazolidinone. Triethylsilane (20 ml, 125 mmol) was added dropwise to a solution of (S)-4-benzyl-3[(1S),(2R)-2-(4-benzyloxyphenyl)-2-hydroxy-1-phenoxyethyl]-2-oxazolidinone (6.5 g, 12.4 mmol). The solution
 was stirred for 1 hour then was diluted with ether, washed
 20 with water (2X), saturated sodium bicarbonate (2X, carefully), dried over magnesium sulfate and concentrated.
 The product was isolated by flash chromatography (hexanes/
 ethyl acetate, 4:1) as an oil (1.8 g).
- C. (S)-4-Benzyl-3-[(1S)-2-(4-hydroxyphenyl)-1phenoxyethyl]-2-oxazolidinone. A solution of (S)-4benzyl-3-[(1S)-2-(4-benzyloxyphenyl)-1-phenoxyethyl]-2oxazolidinone (1.8 g) in ethyl acetate (50 ml) containing
 10% palladium on carbon (1.8 g) was hydrogenated at 40 psi
 overnight. The catalyst was filtered, the solution
 concentrated and the product purified by flash
 chromatography (hexanes/ethyl acetate, 3:2) as an oil
 (0.81 g).
 - D. (S)-4-Benzyl-3-{(1S)-2-[4-(2-phenylethoxy) phenyl]-1-phenoxyethyl}-2-oxazolidinone. To a solution of

- (S)-4-benzyl-3-[(1S)-2-(4-hydroxyphenyl)-1-phenoxyethyl]2-oxazolidinone (0.25 g, 0.60 mmol), phenethyl alcohol (80 ml, 0.66 mmol) and triphenylphosphine (0.17 g, 0.66 mmol) in tetrahydrofuran (5 ml) was added diisopropylazodicarboxylate (0.13 ml, 0.66 mmol). The mixture was stirred overnight in the dark, then concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate, 3:1) as a white solid (0.28 g).
- E. 2-Phenoxy-3-[4-(2-phenyl) ethoxyphenyl]propanoic
 10 acid. A solution of (S)-4-benzyl-3-{(1S)-2-[4-(2-phenylethoxy)phenyl]-1-phenoxyethyl}-2-oxazolidinone (0.28 g, 0.54 mmol) in tetrahydrofuran (10 ml) and 0.5N lithium hydroxide (5 ml) was stirred at 0°C for 3 hours. The mixture was acidified with 1N HCl, diluted with water and extracted with ethyl acetate (3X). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated. The product was isolated by flash chromatography (hexanes/ethyl acetate/acetic acid, 15:5:1) as a white solid, m.p. 96-97°C. [α]_D -1.0° (c 1.76, 20 CHCl₃).

The following compounds were prepared by the same sequence from the appropriate starting materials and reagents.

- (S)-3-{4-[2-(2-Aminophenyl)]ethoxyphenyl}-2-phenoxy-25 propanoic acid, m.p. 100-103°C. $[\alpha]_D$ -9.7° (c 1.17, CHCl₃).
 - (S)-3-{4-[2-(4-Benzyloxyphenyl)]ethoxyphenyl}-2-phenoxypropanoic acid, m.p. 103-105°C. $[\alpha]_D$ +7.60° (c 1.13, CDCl₃).
- 30 (R)-3-{4-[2-(4-Benzyloxyphenyl)]ethoxyphenyl}-2-phenoxypropanoic acid, m.p. 103-105°C. $[\alpha]_D$ -8.16° (c 1.93, CDCl₃).

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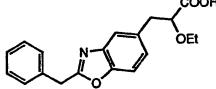
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(S)-3- $\{4-[2-(4-Benzyloxyphenyl)]$ ethoxyphenyl}-2ethoxypropanoic acid (oil). [α]_n +5.82° (c 0.55, CDCl₃).

EXAMPLE 26

2-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propanoic acid



A. 3-(4-Benzyloxy-3-nitrophenyl)-2-ethoxypropanenitrile. This compound was prepared in 3 steps from 4benzyloxy-3-nitrobenzaldehyde according to the procedure described in Example 18.

B. 3-(3-Amino-4-hydroxyphenyl)-2-ethoxypropane
nitrile. A solution of 3-(4-benzyloxy-3-nitrophenyl)-2ethoxypropanenitrile (0.54 g, 1.7 mmol) in ethanol (25 ml)
and acetic acid (75 ml) containing 10% palladium on carbon
(0.40 g) was hydrogenated at 45 psi for 1 hour. The
catalyst was filtered and the solution concentrated. The

15 residue was treated with 5% sodium bicarbonate (100 ml)
and extracted with ethyl acetate (3 X 100 ml). The
combined extracts were washed with water (2 X 100 ml) and
brine (100 ml), dried over sodium sulfate and
concentrated. The product was isolated by column

20 chromatography (silica gel, 2% methanol in chloroform) as
a solid (0.20 g, m.p. 114-115°C)

c. 2-Ethoxy-3-(4-hydroxyphenyl-3-benzamido) propanenitrile. A mixture of 3-(3-amino-4-hydroxyphenyl)-2-ethoxypropanenitrile (0.26 g, 1.2 mmol), phenylacetic acid (0.17 g, 1.2 mmol) and dicyclohexylcarbodiimide (0.25 g, 1.2 mmol) in dimethylformamide (0.5 ml) and tetrahydrofuran (15 ml) was stirred at room temperature for 14 hours. The solution was concentrated, the residue taken up in ethyl acetate (75 ml), this mixture was filtered and the filtrate was washed with water (3 X 25 ml) and brine (25 ml), dried over sodium sulfate and concentrated. The

product was isolated by column chromatography (silica gel, chloroform) as an oil (0.21 g).

- D. 2-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propanenitrile. A solution of 2-ethoxy-3-(4-hydroxyphenyl-35 benzamido)propanenitrile (83 mg, 0.26 mmol) and pyridinium
 p-toluenesulfonate (15 mg, 63 mmol) in xylenes (10 ml) was
 heated to reflux for 9 hours, then cooled, diluted with
 ethyl acetate (65 ml), washed with water (3 X 25 ml) and
 brine (25 ml), dried over sodium sulfate and concentrated.

 10 The product was isolated by column chromatography (silica
 gel, chloroform) as a yellow oil that solidified on
 standing (50 mg).
- E. 2-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propanoic
 acid. 2-Ethoxy-3-(2-benzyl-5-benzoxazolyl)propanenitrile
 was hydrolyzed as described in Example 18.

HRMS: Calc. 325.1314 Found 325.1288

The following compounds were prepared by the same sequence from the appropriate starting materials and 20 reagents.

3-[2-(4-Benzyloxybenzyl)-5-benzoxazolyl]-2-ethoxy-propanoic acid.

HRMS: Calc. 431.1738 Found 431.1732

25 2-Ethoxy-3-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)-5-benzoxazolyl]propanoic acid.

HRMS: Calc. 406.1533 Found 406.1528

2-Ethoxy-3-[2-(2-pyridylmethyl)-5-benzoxazolyl]

30 propanoic acid.

HRMS: Calc. 326.1270 Found 326.1266

15

25

CLAIMS

1. A compound of the formula

$$z \xrightarrow{x} x \xrightarrow{z^1} x \xrightarrow{coy^1}$$

wherein:

A is

$$\begin{pmatrix} (CH_2) \\ 0 \end{pmatrix} \qquad \qquad \begin{pmatrix} (CH_2) \\ 1 \end{pmatrix} \qquad \qquad or \qquad \begin{pmatrix} N \\ 1 \end{pmatrix} \qquad \qquad 0$$

n is 0 or 1;

--- represents a bond or no bond;

R is C1 to C8 alkyl, C3 to C7 cycloalkyl, C3 to C8 alkenyl, C3 to C8 alkynyl, phenyl, C7 to C8 phenylalkyl, C2 to C8 alkanoyl, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro;

X is S, O, NR², -CH=CH-, -CH=N- or -N=CH-; R² is hydrogen, C1 to C3 alkyl, phenyl or benzyl; Y is CH or N;

Z is hydrogen, C1 to C7 alkyl, C3 to C7 cycloalkyl, phenyl, or phenyl mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, C1 to C3 alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

20 X^1 is 0, S, SO or SO₂;

Y¹ is hydroxy, C1 to C3 alkoxy, phenoxy, benzyloxy, amino, C1 to C4 alkanoylamino, C1 to C4 alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di(C1 to C3 alkyl)aminosulfonylamino, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro; and

Z1 is hydrogen or C1 to C3 alkyl;

a pharmaceutically acceptable cationic salt thereof 30 when Y¹ is hydroxy; or

a pharmaceutically acceptable acid addition salt thereof when the compound contains a basic nitrogen atom.

2. A compound according to Claim 1 wherein:

--- represents no bond;

X is 0 and Y is N, together forming an oxazol-4-yl group;

Z is phenyl, substituted at the 2-position of the oxazole ring; and

 \mathbf{Z}^1 is methyl, substituted at the 5-position of the oxazole ring.

3. A compound according to Claim 2 wherein:

10 X^1 is S;

Y' is hydroxy;

A is

; and

R is C1 to C4 alkyl, phenyl or benzyl.

4. A compound according to Claim 2 wherein:

 X^1 is 0;

Y' is hydroxy;

A is

; and

20 R is C1 to C4 alkyl, phenyl or benzyl.

5. A compound according to Claim 2 wherein:

 X^1 is 0;

Y1 is hydroxy;

A is

; and

R is C1 to C4 alkyl, phenyl or benzyl.

25

6. A compound according to Claim 1 wherein:--- represents no bond;

X is -CH=CH-;

Y is -CH-;

Z1 is hydrogen;

 X^1 is 0; and

Y¹ is hydroxy.

7. A compound according to Claim 6 wherein:

Z is hydrogen, benzyloxy or m-fluorobenzyloxy; and

10 R is C1 to C4 alkyl, phenyl or benzyl.

B. A compound according to Claim 7 wherein:

Z is benzyloxy or m-fluorobenzyloxy; and

A is

- 9. A compound according to Claim 8 wherein Z is 4-benzyloxy or 4-m-fluorobenzyloxy.
 - 10. A compound according to Claim 7 wherein:

Z is 4-benzyloxy; and

A is

20

11. A compound according to Claim 7 wherein R:

A is

; and

R is C1 to C4 alkyl, phenyl or benzyl.

15

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12. A compound according to Claim 1 wherein:

--- represents no bond;

X is -CH=CH- and Y is N, together forming a 2pyridyl group;

Z is hydrogen;

X1 is 0; and

Y' is hydroxy.

13. A compound according to Claim 12 wherein: Z^1 is methyl, substituted at the 5-position of the 10 pyridine ring;

A is

; and

R is phenyl.

14. A compound according to Claim 12 wherein:

Z¹ is hydrogen;

A is

: and

R is ethyl.

15. A compound according to Claim 1 wherein:

--- represents a bond;

X is O and Y is N, together forming an oxazol-4-yl group;

Z is phenyl, substituted at the 2-position of the oxazole ring; and

 Z^1 is methyl, substituted at the 5-position of the oxazole ring.

16. A compound according to Claim 15 wherein:

 X^1 is 0;

Y' is NH2;

A is

5

15

R is phenyl.

17. A compound of the formula

wherein:

W is O, CO, CH2, CHOH or -CH=CH-;

10 m is 0, 1 or 2;

--- represents a bond or no bond;

R is C1 to C8 alkyl, C3 to C7 cycloalkyl, C3 to C8 alkenyl, C3 to C8 alkynyl, phenyl, C7 to C8 phenylalkyl, C2 to C8 alkanoyl, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro;

X is S, O, NR², -CH=CH-, -CH=N- or -N=CH-; R² is hydrogen, C1 to C3 alkyl, phenyl or benzyl; Y is CH or N;

Z is hydrogen, C1 to C7 alkyl, C3 to C7 cycloalkyl, phenyl, or phenyl mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, C1 to C3 alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

 X^1 is 0, S, SO or SO₂;

25 Y¹ is hydroxy, C1 to C3 alkoxy, phenoxy, benzyloxy, amino, C1 to C4 alkanoylamino, C1 to C4 alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di(C1 to C3 alkyl)aminosulfonylamino, or one of said groups mono- or disubstituted with C1 to C3 alkyl, tri-

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fluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro; and

Z1 is hydrogen or C1 to C3 alkyl;

a pharmaceutically acceptable cationic salt thereof when Y^1 is hydroxy; or

a pharmaceutically acceptable acid addition salt thereof when the compound contains a basic nitrogen atom.

18. A compound according to Claim 17 wherein:

m is 2; and

- 10 X is O and Y is N, together forming an oxazol-4-yl group.
 - 19. A compound according to Claim 18 wherein:

W is 0 or CO;

m is 2;

R is C1 to C4 alkyl or C2 to C8 alkanoyl;

Z is phenyl, substituted at the 2-position of the oxazole ring;

 X^1 is S or O;

Y' is OH; and

- 20 Z¹ is methyl, substituted at the 5-position of the oxazole ring.
 - 20. A compound according to Claim 19 wherein:

W is 0;

R is methyl; and

 X^1 is S.

21. A compound according to Claim 19 wherein:

W is 0;

--- represents no bond;

R is acetyl; and

 X^1 is S.

22. A compound according to Claim 19 wherein:

W is CO;

--- represents a bond;

R is methyl; and

5 X^1 is S.

23. A compound according to Claim 19 wherein:

W is CO;

--- represents no bond;

R is ethyl; and

10 X^1 is 0.

24. A compound according to Claim 17 wherein:

m is 2;

X is -CH=CH-; and

Y is -CH-.

15 25. A compound according to Claim 24 wherein:

W is 0;

--- represents no bond;

 X^1 is 0;

Y' is OH; and

20 Z¹ is hydrogen.

26. A compound according to Claim 25 wherein:

R is C1 to C4 alkyl, phenyl or benzyloxy; and

Z is hydrogen, benzyloxy or fluorobenzyloxy.

27. A compound according to Claim 26 wherein:

25 R is phenyl; and

Z is hydrogen, 4-benzyloxy or 4-m-fluorobenzyloxy.

28. A compound according to Claim 26 wherein:

R is methyl or ethyl; and

Z is 4-benzyloxy or 4-m-fluorobenzyloxy.

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- 29. A compound according to Claim 26 wherein:
- R is benzyloxy; and
- Z is 4-benzyloxy.
- 30. A compound according to Claim 17 wherein:
- 5 m is 3; and

X is -CH=CH- and Y is N, together forming a 2-pyridyl group.

31. A compound according to Claim 30 wherein: W is O;

W 15 0

10 --- represents no bond;

R is C1 to C4 alkyl;

Z is ethyl, substituted at the 5-position of the
pryridyl ring;

 X^1 is 0;

15 Y^1 is OH; and

Z¹ is hydrogen.

- 32. A compound according to one of Claims 1, 2 or 17 wherein --- represents no bond and which is optically active.
- 20 33. A pharmaceutical composition for use in a hyperglycemic mammal which comprises a blood glucose lowering amount of a compound according to Claim 1, 4, 8, 17 or 26.
- 34. A method of lowering the blood glucose in a
 25 hyperglycemic mammal which comprises administering to
 said mammal a blood glucose lowering effective amount of
 a compound according to Claim 1, 4, 8, 17 or 26.
- 35. A pharmaceutical composition for use in a hypercholesterolemic mammal which comprises a blood cholesterol lowering amount of a compound according to Claim 1, 4, 8, 17 or 26.

- 36. A method of lowering the blood cholesterol in a hypercholesterolemic mammal which comprises administering to said mammal a blood cholesterol lowering effective amount of a compound according to Claim 1, 4, 8, 17 or 26.
- 37. A process for preparing a compound of the formula

$$z \xrightarrow{x} x \xrightarrow{z^1} x \xrightarrow{x^1_R} x$$

or

$$z \xrightarrow{X}_{Z^{1}}^{(CH_{2})_{m}} w \xrightarrow{X^{1}_{R}}^{COY^{1}}$$

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wherein A is

n is 0 or 1;

m is 0, 1 or 2;

15 --- represents a bond or no bond;

R is C1 to C8 alkyl, C3 to C7 cycloalkyl, C3 to C8 alkenyl, C3 to C8 alkynyl, phenyl, C7 to C8 phenylalkyl, C2 to C8 alkanoyl, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl,

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20 hydroxy, C1 to C3 alkoxy, fluoro or chloro; W is O, CO, CH₂, CHOH or -CH=CH-;

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X is S, O, NR², -CH=CH-, -CH=N- or -N=CH-; R² is hydrogen, C1 to C3 alkyl, phenyl or benzyl; Y is CH or N;

Z is hydrogen, C1 to C7 alkyl, C3 to C7 cycloalkyl, phenyl, or phenyl mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, C1 to C3 alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

X1 is 0, S, SO or SO;

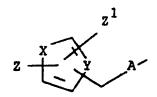
Y¹ is hydroxy, C1 to C3 alkoxy, phenoxy, benzyloxy, amino, C1 to C4 alkanoylamino, C1 to C4 alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di(C1 to C3 alkyl)aminosulfonylamino, or one of said groups mono- or disubstituted with C1 to C3 alkyl, trifluoromethyl, hydroxy, C1 to C3 alkoxy, fluoro or chloro; and

Z1 is hydrogen or C1 to C3 alkyl;

a pharmaceutically acceptable cationic salt thereof when Y^1 is hydroxy; or

a pharmaceutically acceptable acid addition salt thereof when the compound contains a basic nitrogen atom, comprising:

(a) when --- represents a bond, X^1 is S and Y^1 is hydroxy, an aldehyde of the formula R'CHO, wherein R' is



when a compound of Formula I is desired, or is

when a compound of Formula II is desired, wherein m, A, W, X, Y, Z and Z¹ are as defined above, is condensed with thiazolidine-4-one-2-thione in the presence of a secondary amine in a reaction-inert solvent and the

3.

resulting thiazolidine is transformed into the final product by reaction with a compound of the formula ROH, wherein R is as defined above;

- (b) when --- represents a bond and X¹ is 0, a

 compound of the formula CH₂=COR-CN or CH₂=COR-COY¹, wherein
 R and Y¹ are as defined above except that Y¹ is not
 hydroxy, is converted to its sodium salt by reaction with
 NaH in a reaction-inert solvent, the resulting salt is
 condensed with an aldehyde of the formula R'CHO, where R'

 is as defined above, to form a compound of the formula
 R'CH=C(OR)CN or R'CH=C(OR)COY¹, respectively, which
 compound is then, if of the formula R'CH=C(OR)COY¹,
 optionally hydrolyzed to the corresponding acid, or, if
 of the formula R'CH=C(OR)CN, is converted to a compound
 of the formula R'CH=C(OR)COY¹ or to the corresponding
 acid;
 - (c) when --- represents no bond, the compounds prepared by (a) and (b) above are reduced to the corresponding product;
- (d) when --- represents no bond and X¹ is S, a nitrile of the formula R'CH₂CH(X²)CN, or an ester of the formula R'CH₂CH(X²)COOR¹, wherein R' is as defined above, X² is a nucleophilically displaceable group and R¹ is an ester forming group, is transformed into the corresponding desired product by nucleophilic displacement of the group X² with RS⁻, wherein R is as defined above, with the concurrent or subsequent conversion of the nitrile or ester group to the group -COY¹;
- (e) when --- represents no bond and X¹ is O, an α-30 hydroxy ester of the formula R'CH₂CHOHCOOR¹ or a cyanhydrin of the formula R'CH₂CH(OR²)CN, wherein R', R¹ and R² are as defined above, is converted to an ester of the formula R'CH₂CH(OR)COOR¹ or the corresponding acid of the formula R'CH₂CH(OR)COOH.

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-77-

38. A process according to Claim 37 wherein:
in (a), said secondary amine is piperidine or
pyrrolidine, said reaction-inert solvent is ethanol and
said condensation reaction occurs at between 40 and
100°C;

in (b), said reaction-inert solvent is dimethylformamide, said reaction with NaH occurs at between 25 and 60°C, said condensation reaction occurs at between 50 and 100°C and said hydrolyzation reaction takes place under aqueous basic conditions;

in (c), said catalyst is Pd/C, Rh/C or Rh(Ph₃P)₃Cl, said reaction-inert solvent is ethanol, and said hydrogenation takes place at a temperature between ambient temperature and 80°C and a pressure between ambient pressure and 125 psig;

in (d), said nucleophilically displaceable group is I, Cl, Br or OSO_2CH_3 , R^1 is C1 to C3 alkyl, Y^1 is alkoxy, and said nitrile conversion takes place by reacting the nitrile with dry HCl in an excess of the corresponding alkanol at a temperature between 15 and 45°C; or

in (e), said α -hydroxy ester conversion comprises reacting said ester, when RO is an ester, by reaction with an activated acid in the presence of at least one equivalent of a tertiary amine, or, when RO is an ether, by reaction with NaH under anhydrous conditions in a reaction-inert solvent to form the sodium salt thereof, which in turn is either coupled with a mesylate ester or halide under anhydrous nucleophilic displacement conditions to form said corresponding ester or under hydrous nucleophilic displacement conditions to form said corresponding acid, and said cyanhydrin conversion comprises conversion of the nitrile group to the corresponding acid by the action of NaOH in an aqueous solvent or to the corresponding ester by the action of dry HCl in an excess of an alcohol of the formula $\mathbb{R}^{1}\text{OH}$,

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wherein R' is C1 to C3 alkyl.

39. A process according to Claim 38 wherein, in (e), said activated acid is an acid chloride or mixed anhydride.

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INTERNATIONAL SEARCH REPORT

International Applica. No PCT/US 91/03858

			S 91/03858		
	N OF SUBJECT MATTER (if several classification				
Int.C1.5 C 07 D 31 C 07 C 69	1/58 A 01 N 31/35 C (Classification and IPC 61 K 31/425 C 07 D 413/ 07 D 263/56 C 07 C 59/			
II. FIELDS SEARCI					
	Minimum Docum	nentation Searched ⁷			
Classification Syste	tn .	Classification Symbols			
Int.C1.5	C 07 D 263/00 C 07 C 59/00	C 07 D 413/00 C 07 D 3	11/00		
	Documentation Searched othe to the Extent that such Documents	er than Minimum Documentation s are Included in the Fields Searched ⁸			
	CONSIDERED TO BE RELEVANT 9		Relevant to Claim No.13		
Category °	Citation of Document, 11 with indication, where approp	riate, of the relevant passages 12	Relevant to Claim No.		
A	EP,A,0177353 (TAKEDA) 9 Apr see claims	ril 1986,	1,17,33 ,35		
A	EP,A,0299620 (BEECHAM) 18 3	1,17,33 ,35			
A	WO,A,8908651 (PFIZER INC.) September 1989, see claims (application)	1,17,33 ,35			
A	WO,A,8908650 (PFIZER INC.) September 1989, see claims (application)	1,17,33 ,35			
"A" document of considered	ries of cited documents : ¹⁰ lefining the general state of the art which is not to be of particular relevance	"T" later document published after the intern or priority date and not in conflict with t cited to understand the principle or theor invention	y underlying the		
filing date "L" document v which is cit	ment but published on or after the international which may throw doubts on priority claim(s) or ed to establish the publication date of another	cannot be considered novel or cannot be involve an inventive step "Y" document of particular relevance; the cla	Y document of particular relevance; the claimed invention		
"O" document other mean	other special reason (as specified) referring to an oral disclosure, use, exhibition or us s bublished prior to the international filing date but	cannot be considered to involve an inven document is combined with one or more ments, such combination being obvious t in the art.	other such docu- o a person skilled		
	the priority date claimed	"&" document member of the same patent far	nny		
IV. CERTIFICATI	ON		18-4		
Date of the Actual	Completion of the International Search 28-08-1991	Date of Mailing of this International Sea	SEP 1991		
International Searce		Signature of Authorized Office.	1		
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET	┛
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	4
V. X OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1	
This International, search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	7
1. Claim numbers *) because they relate to subject matter not required to be searched by this	
Authority, namely:	
*) 34,36	
See PCT-Rule 39.1 (iv): methods for treatment of the human	- 1 ;
or animal body by surgery or therapy as well as diagnostic	
methods	
	1
2. Claim numbers because they relate to parts of the International application that do not comply	
with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:	
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3. Utaim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).	-
VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2	٦
	ヿ゙
This International Searching Authority found multiple Inventions in this International application as follows:	-
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1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims	-
of the International application	-
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only	1
those claims of the International application for which fees were paid, specifically claims:	- 1
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3. Who required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: It is covered by claim numbers:	1
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A D all correlable claims could be correlated without affect institutions and different feet the International Correlation Authority did and	
As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.	
As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee. Remark on Protest	
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9103858

 SA 48615

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/91

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
EP-A- 0177353	09-04-86	WO-A- WO-A- AU-B- AU-A- CA-A-	8602073 8606069 583537 4817685 1263655	10-04-86 23-10-86 04-05-89 10-04-86 05-12-89	
EP-A- 0299620	18-01-89	AU-A- JP-A-	1767588 1013088	15-12-88 17-01-89	
WO-A- 8908651	21-09-89	EP-A-	0332332	13-09-89	
WO-A- 8908650	21-09-89	EP-A-	0332331	13-09-89	

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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Application No.: 10/700,417 Appeal Brief

EVIDENCE APPENDIX

Application No.: 10/700,417 Appeal Brief

EVIDENCE APPENDIX

1. Final Office Action (entered into the record and mailed by the Examiner on August 17, 2005).

- 2. WIPO International Publication No.: WO 91/19702 ("Hulin") (entered into the record by the Examiner in the Office Action mailed February 25, 2005).
- 3. WIPO International Publication No.: WO 02/16331 ("Brooks") (entered into the record by the Examiner in the Office Action mailed February 25, 2005).





UNITED STATE ATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FI	LING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.	
10/700,417		11/04/2003	Alfred Binggeli	21477	5814	
151	7590	08/17/2005		EXAMINER		
HOFFMAN	N-LA R	OCHE INC.		STOCKTO	N, LAURA	
PATENT LA 340 KINGSI				ART UNIT	PAPER NUMBER	
NUTLEY, 1				1626		

DATE MAILED: 08/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

STATUTORY PERIOD EXPIRES: 326. 17, 2005

AUG 19 2005

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		Application No.	Applicant(s)					
		10/700,417	BINGGELI ET AL.					
Office Action Summary	/	Examiner	Art Unit					
		Laura L. Stockton, Ph.D.	1626					
The MAILING DATE of this come Period for Reply	The MAILING DATE of this communication appears on the cover sheet with the correspondence address							
A SHORTENED STATUTORY PERIO THE MAILING DATE OF THIS COMM - Extensions of time may be available under the provi after SIX (6) MONTHS from the mailing date of this - If the period for reply specified above is less than th - If NO period for reply is specified above, the maximu - Failure to reply within the set or extended period for Any reply received by the Office later than three mo earned patent term adjustment. See 37 CFR 1.704	SUNICATION. sions of 37 CFR 1.13 communication. irty (30) days, a reply um statutory period w reply will, by statute, nths after the mailing	66(a). In no event, however, may a within the statutory minimum of thi fill apply and will expire SIX (6) MO cause the application to become A	reply be timely filed rty (30) days will be considered timely. NTHS from the mailing date of this commu BANDONED (35 U.S.C. § 133).	unication.				
Status								
1) Responsive to communication(s	1)⊠ Responsive to communication(s) filed on <u>31 May 2005</u> .							
2a)⊠ This action is FINAL .	2b)∏ This	action is non-final.						
• •	3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213.							
Disposition of Claims								
 4) Claim(s) 1-56 is/are pending in the application. 4a) Of the above claim(s) 51 and 54-56 is/are withdrawn from consideration. 5) Claim(s) is/are allowed. 6) Claim(s) 1-12,16-20,22-26,29-35,39-44,46,47,50,52 and 53 is/are rejected. 7) Claim(s) 13-15, 21, 27, 28, 36-38, 45, 48 and 49 is/are objected to. 8) Claim(s) are subject to restriction and/or election requirement. 								
Application Papers			•					
9) The specification is objected to be	y the Examiner	•						
10) The drawing(s) filed on is/	are: a)∏ acce	pted or b) objected to	by the Examiner.					
Applicant may not request that any o	•	• • • • • • • • • • • • • • • • • • • •	• •					
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d). 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.								
Priority under 35 U.S.C. § 119								
 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received. 								
Attachment(s)								
1) Notice of References Cited (PTO-892)			ummary (PTO-413)					
Paper No(s)/Mail Date Paper No(s)/Mail Date Paper No(s)/Mail Date Paper No(s)/Mail Date								

U.S. Patent and Trademark Office PTOL-326 (Rev. 1-04)

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DETAILED ACTION

Claims 1-56 are pending in the application.

Election/Restrictions

Applicants' election with traverse of Group I, and the species of Example 47 on page 67 (named below), in the reply filed on January 10, 2005 was acknowledged in the previous Office Action.

Example 47

a] [rac]-3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-2-methyl-phenyl]-2-ethoxy-propionic acid ethyl ester

[0176] In analogy to the *Mitsunobu*-procedure described in example 1, step f, [rac]-2-ethoxy-3-(4-hydroxy-2-methyl-phenyl)-propionic acid ethyl ester (example 46 b]) was reacted with 2-(2-tert-butyl-5-methyl-oxazol-4-yl)-ethanol (example 1, step e]) in the presence of triphenylphosphine and di-tert-butyl azodicarboxylate to yield [rac]-3-{4-[2-(2-tert-butyl-5-methyl-oxazol-4-yl)-ethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid ethyl ester as colorless oil.

MS: 440.4 (M+Na)⁺, 418.4 (M+H)⁺, 374.4, 349.4, 282.3, 226.3.

b] [rac]-3-{4-[2-(2-tert-Butyl-5-methyl-oxazol-4-yl)-ethoxy]-2-methyl-phenyl}-2-ethoxy-propionic acid

The requirement was deemed proper and made FINAL in the previous Office Action.

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Claims 51 and 54-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on January 10, 2005.

Rejections made in the previous Office Action that do not appear below have been overcome. Therefore, arguments pertaining to these rejections will not be addressed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

⁽a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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Claims 1-12, 16-20, 22-26, 29-35, 39-44, 46, 47, 50, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hulin {WO 91/19702}, taken alone, or in combination with the teachings of Brooks et al. {WO 02/16331}.

Determination of the scope and content of the prior art (MPEP \$2141.01)

Applicants claim oxazole compounds. Hulin teaches oxazole compounds that are structurally similar to the instant claimed compounds. See in Hulin (pages 6-7), for example, Formula (II) wherein Z is alkyl; Z¹ is alkyl; X is O; Y is N; m is 2; W is O; ----- represents no bond; X¹ is O; R is alkyl; and Y¹ is hydroxy. Also note Example 13 on page 39.

Ascertainment of the difference between the prior art and the claims (MPEP \$2141.02)

The difference between the compounds of Hulin and the instant claimed compounds is that of a hydrogen (in the teaching of Hulin) versus a homolog such as a

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methyl group (instant R^3-R^6 variables, note proviso) attached to the phenyl ring in instant formula (I).

Finding of prima facie obviousness--rational and motivation (MPEP \$2142-2413)

To those skilled in chemical art, one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. In re Henze, 85 USPQ 261 (1950). Additionally, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. In re Wood, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lohr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., a hypoglycemic agent).

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Alternatively, Brooks et al. teach the interchangeability of hydrogen versus an alkyl group on said phenyl ring in hypoglycemic agents. See in Brooks et al. the definition of the Y variable on page 4 (e.g., unsubstituted or substituted phenylene); the possible substituents on the phenylene found on page 6, lines 28-30; the use on page 5; and especially Example 14 on page 83.

The instant claimed compounds would have been obvious because one skilled in the art would have been motivated to prepare homologs of the compounds taught in Hulin, or alternatively, especially in view of the teachings of Brooks et al., to arrive at the instant claimed compounds with the expectation of obtaining compounds which could be used as hypoglycemic agents. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

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Response to Arguments

Applicants' arguments filed May 31, 2005 have been considered. Applicants argue that a prima facie case of obviousness has not been established because there is absolutely no motivation to modify Hulin to obtain the compounds of the instant invention. Applicants argue that there is no motivation to modify the compounds of Hulin because: (1) all the generic structures and species in Hulin (and in Brooks et al.) are extremely broad and/or different; and (2) the utilities or properties of the compounds disclosed in Hulin and the claimed invention are different.

In response, Applicants' arguments have been considered but have not been found persuasive. Hulin teaches oxazole compounds that are structurally similar to the instant claimed compounds. See in Hulin (pages 6-7), for example, Formula (II) wherein Z is alkyl; Z¹ is alkyl; X is O; Y is N; m is 2; W is O; -----

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represents no bond; X^1 is O; R is alkyl; and Y^1 is hydroxy. Especially note Example 13 on page 39.

Further, Hulin teach that their oxazole compounds are useful as, hypocholesterolemic agents (page 1, lines 5-9), one of the same utilities Applicants disclose. See paragraph [0039] on page 14 and paragraph [0044] on page 16 of the instant specification. Additionally, there is no requirement that the prior art must suggest that the claimed product will have the same or similar utility as that discovered by applicant in order to support a legal conclusion of obviousness. *In re Dillon*, 16 U.S.P.Q. 2d 1897, 1904 (Fed. Cir. 1990). Therefore, there is sufficient motivation to modify the compounds of Hulin.

Applicants argue that: (1) the compounds of Formula (I) in Hulin are structurally different; (2) 1/12 or 8.3% of the compounds embraced by formula (II) in Hulin relate to oxazoles; (3) the central phenyl moiety of the compounds of Hulin are unsubstituted whereas in the

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instant claimed compounds the central phenyl moiety is substituted; (4) the variables in Hulin (i.e., R, X, Y, Z, etc.) are much different and/or extremely broad; and (5) Brooks et al. disclose a very broad and different generic structure.

In response, firstly, Formula (I) in Hulin was not relied upon in making the rejection of the instant claims under 35 USC 103. Secondly, the total number of specific specie prepared in a prior art reference is not a determining factor in establishing a prima facie case of obviousness. It is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to person of ordinary skill in the art. In re Boe, 148 USPQ 507, 510 (CCPA 1966).

Thirdly, and as stated above, the difference between the compounds of Hulin and the instant claimed

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compounds is that of a hydrogen (in the teaching of Hulin) versus a homolog such as a methyl group (instant R³-R⁶ variables, note proviso) attached to the phenyl ring in instant formula (I) in claim 1. Fourth and fifthly, although the disclosures in Hulin and Brooks et al. may be perceived as broad to Applicants, the motivation to prepare additional compounds embraced by Hulin lies in the fact that both Hulin and Brooks et al. prepare specie which differ from the instant claimed compounds at only one or two positions (see Example 13 on page 39 in Hulin and Example 14 on page 83 in Brooks et al.). If not for this difference in each of the prior art references specifically prepared specie, the instant claims would have also been rejected under 35 USC 102(b).

Applicants argue that: (1) there are no teachings of similar properties or uses in Hulin and the presently claimed invention because the instant claimed compounds bind to and activate the peroxisome

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proliferator activated receptors PPAR-alpha and PPAR-gamma; and (2) proper motivation to combine the teachings of Hulin and Brooks et al. has not been established.

All of Applicants' arguments have been considered but have not been found persuasive. As stated above, there is no requirement that the prior art must suggest that the claimed product will have the same or similar utility as that discovered by applicant in order to support a legal conclusion of obviousness. In re Dillon, 16 U.S.P.Q. 2d 1897, 1904 (Fed. Cir. 1990). Applicants are arguing the mode of action. However, the same end result and the same patients are being treated by Hulin and by the method disclosed by Applicants in the instant specification (i.e., treating patients having high cholesterol levels). Therefore, Applicants' arguments are not persuasive.

Applicants argue that there is no motivation to combine the teachings of Hulin and Brooks et al. This

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argument is not persuasive. The test for combining references is not what individual references themselves suggest but rather what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (1971). Each of Hulin (pages 6-7) and Brooks et al. (pages 4-5) teach oxazole compounds that are structurally similar to the instant claimed compounds and each other. of Hulin (page 19, starting at line 31, thru to page 23) and Brooks et al. (page 5, lines 4-14) teach that their oxazole compounds are useful in treating, for example, high cholesterol levels. Brooks et al. even teach that their compounds are peroxisome proliferator activated receptor agonists (page 1, lines 9-23). For all the reasons given above, the instant claimed invention would have been suggested to one skilled in the art.

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The elected species of Example 47 is not allowable over the art of record.

Allowable Subject Matter

Claims 13-15, 21, 27, 28, 36-38, 45, 48 and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the

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mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for

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The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Laura L. Stockton, Ph.D.

Patent Examiner

Art Unit 1626, Group 1620

Technology Center 1600

August 15, 2005

NEW CENTRAL FAX NUMBER

Effective July 15, 2005

On <u>July 15, 2005</u>, the Central FAX Number will change to **571-273-8300**. This new Central FAX Number is the result of relocating the Central FAX server to the Office's Alexandria, Virginia campus.

Most facsimile-transmitted patent application related correspondence is required to be sent to the Central FAX Number. To give customers time to adjust to the new Central FAX Number, faxes sent to the old number (703-872-9306) will be routed to the new number until September 15, 2005. After September 15, 2005, the old number will no longer be in service and 571-273-8300 will be the only facsimile number recognized for "centralized delivery".

CENTRALIZED DELIVERY POLICY: For patent related correspondence, hand carry deliveries must be made to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), and facsimile transmissions must be sent to the Central FAX number, unless an exception applies. For example, if the examiner has rejected claims in a regular U.S. patent application, and the reply to the examiner's Office action is desired to be transmitted by facsimile rather than mailed, the reply must be sent to the Central FAX Number.

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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL,

[Continued on next page]

(54) Title: OXAZOLYL-ARYLPROPIONIC ACID DERIVATIVES AND THEIR USE AS PPAR AGONISTS

(57) Abstract: Compounds represented by the following structural formula (I), and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein: n is 2, 3, or 4 and W is CH₂, CH(OH), C(O) or O; R1 is an unsubstituted or substituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aryl-alkyl, heteroaryl-alkyl, cycloalkyl-alkyl, or t-butyl; R2 is H, alkyl, haloalkyl or phenyl; Y is an unsubstituted or substituted thiophen-2,5-diyl or phenylene; R3 is alkyl or haloalkyl; R4 is a substituted or unsubstituted phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, quinolyl, pyridyl or benzo[1,3]dioxol-5-yl group; and R5 is H, alkyl, or aminoalkyl; are useful for modulating a peroxisome proliferator activated receptor, particularly in the treatment of diabetes mellitus.

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PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR AGONISTS

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BACKGROUND OF THE INVENTION

Peroxisome Proliferator Activated Receptors (PPARs) are 10 members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Various subtypes of PPARs have been discovered. These include PPARa, PPARB or NUC1, PPARy and PPARS.

The PPARa receptor subtypes are reported to be

activated by medium and long-chain fatty acids. They are
involved in stimulating beta-oxidation of fatty acids and
with the activity of fibrates which reportedly produce a
substantial reduction in plasma triglycerides and moderate
reduction in low density lipoprotein (LDL) cholesterol. The

PPARy receptor subtypes are reportedly involved in
activating the program of adipocyte differentiation and are
not involved in stimulating peroxisome proliferation in the
liver.

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Diabetes is a disease in which a mammal's ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. "Type II Diabetes" or "non-insulin dependent diabetes mellitus" (NIDDM) is the form of diabetes which is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the 10 main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin and hyperinsulemia results. Hyperinsulemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL which are risk factors in cardiovascular diseases. The constellation of symptoms which includes hyperinsulemia combined with hypertension, 25 elevated body weight, elevated triglycerides and elevated LDL is known as Syndrome X.

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Current treatment for diabetes mellitus generally first involves treatment with diet and exercise. However, compliance can be poor and as the disease progresses treatment with hypoglycemics, typically sulfonylureas, is often necessary. Sulfonylureas stimulate the β cells of the WO 02/16331 PCT/US01/22616

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liver to secrete more insulin. However, the response of the β cells eventually fails and treatment with insulin injection is necessary. In addition, both sulfonylurea treatment and insulin injection have the life threatening 5 side effect of hypoglycemic coma. Therefore, patients using these treatments must carefully control dosage.

Thiazolidinediones are a class of compounds which have been shown to increase the sensitivity of insulin sensitive cells. Increasing insulin sensitivity rather than the 10 amount of insulin in the blood reduces the likelihood of hypoglycemic coma. Thiazolidinediones have been shown to increase insulin sensitivity by binding to PPARy receptors. However, side effects associated with treatment with thiazolidinediones include weight gain, and, for troglitazone, liver toxicity.

PPARa and PPARy receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as, inflammatory bowel disease. There exists a need for new pharmaceutical agents 20 which modulate these receptors to prevent, treat and/or alleviate these diseases or conditions while ameliorating side effects of current treatments.

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SUMMARY OF THE INVENTION

25 The present invention is directed to compounds represented by Structural Formula I and pharmaceutically acceptable salts, solvates and hydrates thereof:

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Strctural Formula I

In Structural Formula I, n is 2, 3, or 4 and W is CH₂,

5 CH(OH), C(O) or O. R1 is an unsubstituted or substituted
group selected from aryl, heteroaryl, cycloalkyl,
heterocycloalkyl, aryl-C1-C4 alkyl, heteroaryl-C1-C4 alkyl,
cycloalkyl-C1-C4 alkyl, or t-butyl. R2 is H, C1-C4 alkyl,
C1-C4 haloalkyl or phenyl. Y is an unsubstituted or

10 substituted group consisting of thiophen-2,5-diyl or
phenylene. R3 is C1-C4 alkyl or C1-C4 haloalkyl. R4 is a
substituted or unsubstituted phenyl, naphthyl, 1,2,3,4tetrahydronaphthyl, quinolyl, pyridyl or benzo[1,3]dioxol-5yl group. R5 is H, C1-C4 alkyl, or aminoalkyl.

In one embodiment, the present invention also relates to pharmaceutical compositions which comprising at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of modulating a peroxisome proliferator activated receptor by contacting the receptor with at least one compound represented by Structural Formula I, and pharmaceutically acceptable salts, solvates and hydrates thereof

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In a further embodiment, the present invention relates to a method of making a compound represented by Structural Formula I.

The compounds of the present invention and

pharmaceutically acceptable salts, solvates and hydrates
thereof are believed to be effective in treating Syndrome X,
Type II diabetes, hyperglycemia, hyperlipidemia, obesity,
coagaulopathy, hypertension, atherosclerosis, and other
disorders related to Syndrome X and cardiovascular diseases
because they lower one or more of the following in mammals:
glucose, insulin, triglycerides, fatty acids and/or
cholesterol. In addition, the compounds exhibit fewer side
effects than compounds currently used to treat these
conditions.

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DETAILED DESCRIPTION OF THE INVENTION

The terms used to describe the instant invention have the following meanings herein.

As used herein, alkyl groups include straight chained or branched C1-C4 hydrocarbons, which are completely saturated.

Cycloalkyl groups, as used herein, include C3-C8 hydrocarbons, which are partially or completely saturated.

As used herein, aryl groups include carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl).

Heteroaryl groups, as used herein, is an aromatic ring

30 system having at least one heteroatom such as nitrogen,
sulfur or oxygen. Heteroaryl groups include thienyl (also

referred to herein as "thiophenyl"), pyridyl, pyrrolyl, benzofuranyl, isoxazolyl, and pyrimidinyl.

An aryl-C1-C4-alkyl group, as used herein, is an aryl substituent that is linked to a compound by an alkyl group having from one to four carbon atoms.

A heteroaryl-C1-C4-alkyl group, as used herein, is a heteroaryl substituent that is linked to a compound by an alkyl group having from one to four carbon atoms.

A cycloalkyl-C1-C4-alkyl group, as used herein, is a cycloalkyl substituent that is linked to a compound by an alkyl group having from one to four carbon atoms.

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An aminoalkyl group is an alkyl group having from one to six carbon atoms which is substituted with at least one amine represented by -NR12R12 in which each R12 are,

independently, a C1-C6 alkyl or both R12 taken together with the nitrogen to which they are attached form a five or six membered heterocycloalkyl.

A heterocycloalkyl is a non-aromatic ring which contains one or more oxygen, nitrogen or sulfer (e.g., morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine). Preferred heterocycloalkyl group is morpholine.

Substituents for aryl, heteroaryl and cycloalkyl groups include halo, carboxyl, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, cyano, CHO, hydroxyl, C1-C4 alkanoic acid and -C(O)NR13R13 in which each R13, independently, H or a C1-C4 alkyl.

Substituents for thiophen-2,5-diyl and phenylene include H, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl and C1-C4 haloalkoxy.

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Preferably, the compounds of the present invention, and with their respective pharmaceutical compositions, have a structure represented by Structural Formula II:

Structural Formula II

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In Structural Formula II, R1, R2 and R5 are as defined for Structural Formula I while R6 are each, independently, H, C1-C4 alkyl or C1-C4 alkoxy. In addition, R7 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl or phenyl. R8 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl, phenyl or together with the phenyl to which they are bound form naphthyl, 1,2,3,4-tetrahydronaphthyl, quinolyl or benzo[1,3]dioxol-5-yl. Further, R9 is C1-C4 alkyl or C1-C4 haloalkyl.

Examples of compounds having Structural Formula II include, for instance, the compounds described in Examples 1-89 and 92-140.

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More preferably, the compounds of the present invention, and with their respective pharmaceutical compositions, have a structure represented by Structural Formula III:

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Structural Formula III

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In Structural Formula III, R5, R6, R7 and R8 are as defined for Structural Formulas I and II while R10 is an unsubstituted or substituted group selected from 2-thienyl, 3-thienyl, phenyl, cyclohexyl or 1-methyl-cyclohexyl.

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Even more preferably, the compounds of the present invention, and with their respective pharmaceutical compositions, have a structure represented by Structural Formula IV or V.

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Structural Formula IV

Structural Formula V

In Structural Formulas IV and V, R7 and R8 are as defined for Structural Formula II while R11 is H, halo or C1-C4 alkyl.

In an alternate embodiment, the compounds of the present invention, and with their respective pharmaceutical compositions, have a structure represented by Structural Formula VI.

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Structural Formula VI

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In Structural Formula VI, R1, R2, R3, R4 and R5 are as defined for Structural Formula I while V is C, C(OH)or C(O).

The compounds of Structural Formula I contain one or more chiral centers, and exist in different optically active forms. When compounds of Structural Formula I contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired

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enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

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In a more preferred embodiment, the compounds of the present invention are S-enantiomers. In a most preferred embodiment, the compounds are (S)-3-{4-[2-(2-Phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxy-propionic acid, (S)-2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxypropionic acid, and (S)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)ethoxy]-phenyl}-2-methyl-2-p-tolyloxy-propionic acid.

When a compound represented by Structural Formula I has more than one chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Structural Formula I and mixtures thereof.

30 Certain compounds of Structural Formula I may exist in zwitterionic form and the present invention includes each

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zwitterionic form of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I and their salts may exist in more than one crystal form. Polymorphs of compounds represented by Structural Formula I form part of this invention and may be prepared by crystallization of a compound of Structural Formula I under different conditions. For example, using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; various modes of 10 cooling, ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting a compound of Structural Formula I followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, 15 differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Certain compounds of Structural Formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of Structural Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I which are substantially non-toxic to mammals. Typical pharmaceutically-acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as base addition

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salts, respectively. It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically-acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

By virtue of its acidic moiety, a compound of Structural Formula I forms salts with pharmaceutically acceptable bases. Some examples of base addition salts include metal salts such as aluminum; alkali metal salts such as lithium, sodium or potassium; and alkaline earth metal salts such as calcium, magnesium, ammonium, or substituted ammonium salts. Examples of substituted ammonium salts include, for instance, those with lower alkylamines such as trimethylamine, triethylamine; hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2hydroxyethyl) -amine or tri-(2-hydroxyethyl) -amine, cycloalkylamines such as bicyclohexylamine or dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, glucamine, N-methylglucamine; bases of the pyridine type such as pyridine, collidine, quinine or quinoline; and salts of basic amino acids such as lysine and arginine.

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Examples of inorganic bases include, without limitation, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

Compounds of Structural Formula I, which are

30 substituted with a basic group, may exist as salts with
pharmaceutically acceptable acids. The present invention

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includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

These salts may be prepared by methods known to those skilled in the art.

Certain compounds of Structural Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

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Prodrugs are compounds of the present invention, which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, nbutyl, isobutyl, tert-butyl, morpholinoethyl, and N,Ndiethylglycolamido.

Methyl ester prodrugs may be prepared by reaction of the acid form of a compound of Formula I in a medium such as methanol with an acid or base esterification catalyst (e.g.,

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NaOH, H_2SO_4). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol.

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Structural Formula I (in a medium such as dimethylformamide) 4-(2-

chloroethyl)morphine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

The term, "active ingredient" means the compounds generically described by Structural Formula I as well as the salts, solvates, and prodrugs of such compounds.

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The term "pharmaceutically acceptable" means that the carrier, diluent, excipients and salt must be compatible with the other ingredients of the composition, and not deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein.

"Treating" refers to mediating a disease or condition and preventing, or mitigating, its further progression or ameliorate the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of a compound, or of its salt, solvate, hydrate or prodrug thereof, that will elicit the biological or medical response of a tissue, system, or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can

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also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount which is sufficient to modulate a PPAR receptor, such as a PPARa or PPARy receptor, which mediate a disease or condition. Conditions mediated by PPARa or PPARy receptors include diabetes mellitus, cardiovascular disease, Syndrome X, obesity and gastrointestinal disease.

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

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Administration to a human is most preferred. The human to whom the compounds and compositions of the present invention are administered has a disease or condition in which control blood glucose levels are not adequately 15 controlled without medical intervention, but wherein there is endogenous insulin present in the human's blood. Noninsulin dependent diabetes mellitus (NIDDM) is a chronic disease or condition characterized by the presence of insulin in the blood, even at levels above normal, but 20 resistance or lack of sensitivity to insulin action at the tissues. The compounds and compositions of the present invention are also useful to treat acute or transient disorders in insulin sensitivity, such as sometimes occur 25 following surgery, trauma, myocardial infarction, and the like. The compounds and compositions of the present invention are also useful for lowering serum triglyceride levels. Elevated triglyceride level, whether caused by genetic predisposition or by a high fat diet, is a risk factor for the development of heart disease, stroke, and 30 circulatory system disorders and diseases. The physician of

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ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective, non-toxic amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycemic human or non-human mammal in need thereof.

They are useful as therapeutic substances in preventing or treating Syndrome X, diabetes mellitus and related endocrine and cardiovascular disorders and diseases in human or non-human animals.

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The invention also relates to the use of a compound of Formula I as described above, for the manufacture of a medicament for treating a PPAR α or PPAR γ mediated condition, separately or in combination.

A therapeutically effective amount of a compound of Structural Formula I can be used for the preparation of a medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of the present invention (1) typically reduces serum glucose levels, or more specifically HbA1c, of a patient by about

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0.7% or more; (2) typically reduces serum triglyceride levels of a patient by about 20% or more, and (3) increases serum HDL levels in a patient. Preferably, HDL levels will be increased by about 30% or more.

Additionally, an effective amount of a compound of Structural Formula I and a therapeutically effective amount of one or more active agents selected from a group consisting of: antihyperlipidemic agent, plasma HDL-raising agents, antihypercholesterolemic agents, fibrates, vitamins, aspirin, insulin secretogogues, insulin and the like can be used together for the preparation of a medicament useful for the above-described treatments.

Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of the compound or compounds of Structural Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances.

When used herein Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy,

hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with

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diabetes including cardiovascular disease, especially atherosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition which contains a compound of Structural Formula I and one or more additional active agents, as well 10 as administration of a compound of Structural Formula I and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of Structural Formula I or thereof and an insulin secretogogue such as biguanides, 15 thiazolidinediones, sulfonylureas, insulin, or α -glucosidose inhibitors can be administered to the patient together in a .single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, 20 a compound of Structural Formula I and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of atherosclerosis may be wherein a compound of Structural Formula I or salts thereof is administered in combination with one or more of the following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As noted above, the compounds of

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Structural Formula I can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the compounds of Structural Formula I, salts thereof can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α -glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating atherosclerosis.

The compounds of the present invention, and the pharmaceutically acceptable salts, solvates and hydrates thereof, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a

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therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers,

diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the active ingredient which is a compound of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage

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form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically-acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

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Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the invention can also be administered in a targeted drug delivery system,

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such as, for example, in a liposome coated with endothelial cell-specific antibody.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, powders, sachets, granules, dragees, capsules, liquids, elixers, tinctures, gels, emulsions, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

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For oral administration in the form of a tablet or capsule, the active ingredient may be combined with an oral, non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, methyl cellulose, calcium carbonate, calcium phosphate, calcium sulfate, sodium carbonate, mannitol, sorbitol, and the like; together with, optionally, disintegrating agents, such as, without limitation, cross-linked polyvinyl pyrrolidone, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid, or a salt thereof such as sodium alginate, and the like; and, optionally, binding agents, for example, without limitation, gelatin, acacia,

synthetic gums, acacia, tragacanth, sodium alginate,

30 carboxymethyl-cellulose, polyethylene glycol, waxes, and the
like; and, optionally, lubricating agents, for example,
without limitation, magnesium stearate, sodium stearate,

natural sugars, beta-lactose, corn sweeteners, natural and

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stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substance which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

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In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or 15 magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may 20 be added.

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All formulations for oral administration should be in dosages suitable for such administration. Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules.

For parental administration the compounds of the present invention, or salts thereof, can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Formulations for injection may be presented in unit dosage form, such as in ampoules or in multi-dose containers, with an added preservative. compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain

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formulatory agents such as suspending, stabilizing and/or dispersing agents. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that each syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against any contamination. The carrier can be solvent or dispersion medium containing, for example, 10 water, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), propylene glycol and 15 liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

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For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently

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delivered in the form of a dry powder inhaler, or an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

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In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilized solid or paste, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active Ingredient",

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refers to a compound according to Structural Formula I or salts thereof.

Formulation 1

5 Hard gelatin capsules are prepared using the following ingredients:

	Quantity
	(mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

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	Quantity
	(mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

The components are blended and compressed to form tablets each weighing 665~mg

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Formulation 3

An aerosol solution is prepared containing the following components:

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	Weight
Active Ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The Active Ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

15 Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

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The Active Ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of Active Ingredient, are made as follows:

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Active Ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

The Active Ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

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Formulation 6

Suppositories, each containing 225 mg of Active Ingredient, are made as follows:

Active Ingredient	225	mg
Saturated fatty acid glycerides	2,000	mg
Total	2,225	mg

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The Active Ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of Active Ingredient per 5 ml dose, are made as follows:

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Active Ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active Ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution,

20 flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

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Formulation 8

An intravenous formulation may be prepared as follows:

Active Ingredient

100 mg

Isotonic saline

1,000 ml

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The solution of the above materials generally is administered intravenously to a subject at a rate of 1 ml per minute.

10 In yet another embodiment of the compounds of the present invention, the compound is radiolabelled, such as with carbon-14, or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new PPARα and PPARγ agonists.

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SYNTHESIS

Compounds of the present invention have been formed by reacting a 2-(R1-substituted)-5-R2-substituted-oxazol-4-yl ethyl sulfonyl ester with a 3-(4-hydroxyphenyl)-2-R4-oxy-propionic acid or a 3-(5-hydroxy-thiophen-2,5-diyl)-2-R4-oxy-propionic acid. Generally, the sulfonyl ester chemical intermediates have been synthesized through two different routes, shown in Schemes IA and IB, while Scheme II is typical of the synthethic method used to make the propionic acid chemical intermediate. The formation of the compounds of the present invention from these chemical intermediates is shown in Scheme III.

In Scheme IA, the first step is a condensation of a dionemonooxime represented by Structural Formula IA-1 with a

R1-substituted aldehyde represented by Structural Formula IA-2 in the presence of an acid such as aqueous concentrated hydrochloric acid or, preferably, acetic acid which is saturated with hydrogen chloride gas. Typically, hydrogen chloride is bubbled through a solution of the dionemonooxime and the R1-substituted aldehyde in acetic acid, which is held at a constant temperature of about 0 °C to about 20 °C for about 15 minutes to about 1 hour. The product of the condensation is an oxazole n-oxide represented by Structural Formula IA-3.

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The oxazole n-oxide is then treated with phosphorous oxyhalide, such as phosphorous oxychloride or phosphorous oxybromide in an inert solvent such as dichloromethane or chloroform to form a 2-(R1-substituted)-4-halomethyl-oxazole represented by Structural Formula IA-4. The reaction typically is carried out at the reflux temperature of the solvent used and is complete in about 15 minutes to about 1 hour.

The 2-(R1-substituted)-4-chloromethyl-oxazole is then treated with a cyanide and an iodide salt to form a 2-(R1-substituted)-4-cyanomethyl-oxazole represented by Structural Formula IA-5. The reaction is typically carried out in a polar, aprotic solvent such as dimethylformamide at a temperature of about 30°C to about 120°C for about 1 hour to about 6 hours. Preferably, the cyanide and iodide salts are potassium cyanide and potassium iodide.

The cyano group of the a 2-(R1-substituted)-4-cyanomethyl-oxazole is converted to a carboxylic acid group by treatment with a alkali metal hydroxide to form a 2-(R1-substituted)-4-carboxymethyl-oxazole represented by Structural Formula IA-6. The reaction is generally carried out in an aqueous solution at about 80°C to about 100°C.

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The concentration of the alkali metal hydroxide in the aqueous solution is typically about 25% to about 85% (weight/volume). Preferably, the alkali metal hydroxide is potassium hydroxide.

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The 2-(R1-substituted)-4-carboxymethyl-oxazole is then treated with a carboxylic acid reducing agent, such as borane or lithium aluminum hydride, to form the 2-(R1substituted) -4-(2-hydroxyethyl) -oxazole intermediate represented by Structural Formula IA-7. The reaction is 10 typically carried out under anhydrous conditions in an ether solvent such as tetrahydrofuran (THF), dioxane, or ethyl ether. When borane is the reducing agent used, it typically forms a complex with the ether solvent such as a BH3-THF complex. A solution having a concentration of about 0.5 M to about 1.5 M borane complex in the ether solvent is added dropwise to a solution of 0.1 M to 1.3 M of the 2-(R1substituted) -4-carboxymethyl-oxazole in the ether solvent. The reaction temperature is about 20°C to about 40°C. Typically, the reaction is complete in about 1 hour to about 5 hours.

The chemical intermediate, represented by Structural Formula IA-7, is then converted into a 2-(R1-substitutedoxazol-4-yl)ethyl sulfonyl ester represented by Structural Formula IA-8 by treatment with a sulfonyl anhydride, such as tosyl anhydride or mesyl anhydride, or a sulfonyl halide, such as tosyl chloride or mesyl chloride, in the presence of a base. The reaction is typically carried out in an aprotic solvent such as methylene chloride in the presence of an aprotic base such as pyridine or N,N-dimethylaminopyridine (DMAP). The reaction is complete in about 0.5 hours to about 5 hours.

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In Scheme IB, the first step is a condensation of •methyl L-aspartate represented by Structural Formula IB-1
with a R1-substituted acid chloride in the presence of mild
base to form the amide represented by Structural Formula IB3. Typically, the reaction is carried out in an
acetone/water media in the presence of a carbonate base,
such as potassium or sodium carbonate. The R1-substituted
acid chloride is added to a solution of •-methyl L-aspartate
in acetone/water at about 0°C to about 10°C and the reaction
warms to ambient temperature for about 60 minutes to 2
hours.

The acid is then treated with a base such as pyridine and an anhydride such as acetic, n-propyl or trifluoro-acetic anhydride to form the R2-substituted ketone represented by Structural Formula IB-4. The reaction is typically carried out at 90°C and is complete in about 90 minutes to about 2 hours.

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Cyclo-dehydration of the R2-substituted ketone is completed with a protic acid such as sulfuric acid in the presence of acetic anhydride to form the 2-(R1-substituted)-5-(R2-substituted)-oxazole represented by Structural Formula IB-5. Alternatively, the ketone can be treated with a phosphorus oxyhalide, such as phosphorous oxychloride or phosphorous oxybromide in a polar, aprotic solvent such as dimethylformamide. In both methods, the reaction is heated to about 90°C and is complete in about 15 minutes to 30 minutes.

The 2-(R1-substituted)-5-(R2-substituted)-oxazole is treated with aqueous base, such as aqueous sodium hydroxide in an alcohol solvent at about 25°C to about 45°C for about 30 minutes to form the corresponding acid. The acid is treated with a carboxylic acid reducing agent, such as borane or lithium aluminum hydride, to form the 2-(R1-substituted)-4-(2-hydroxyethyl)-oxazole intermediate represented by Structural Formula IA-7. The reaction is typically carried out as described for the formation of the

intermediate represented by Structural Formula IA-7 in Scheme IA.

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The compound represented by Structural Formula II-7 can be prepared by the method depicted in Scheme II. In this method, an α -bromoester represented by compound II-1 is reacted with a phenol represented by compound II-2 to form an α -phenoxy ester represented by compound II-3. This reaction is typically carried out in an anhydrous polar solvent such as DMF at a temperature of about 60°C to about 110° C. The reaction time is about 10 h to about 20 h.

The α-phenoxy ester is then deprotonated with an alkylamide lithium compound, such as LDA (1.1 eq), to form the enol. This reaction is typically performed in an anhydrous, polar, aprotic solvent at a temperature of about -20°C to about -110°C. After about 5 min to about 20 min. a 4-benzyloxybenzaldehyde represented by compound II-4 is added and the reaction is stirred for about 5 min. to about 30 min., then quenched with an aqueous solution of ammonium chloride to form a 3-(4-benzyloxyphenyl)-3-hydroxy-2-substituted-2-phenoxy-propanoic ester represented by Structure II-5.

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A solution of 3-(4-benzyloxyphenyl)-3-hydroxy-2-substituted-2-phenoxy-propanoic ester in an anhydrous aprotic solvent at a temperature of about -10 °C to about 10 °C was treated with an ether complex of boron trifluoride and triethylsilane. The reaction is gradually allowed to warm to room temperature then stirred for about 1 h to about 2.5 h. The mixture is quenched by adding an aqueous base to form 3-(4-benzyloxyphenyl)-2-substituted-2-phenoxy-propanoic ester represented by Structural Formula II-6.

The compound represented by Structural Formula II-6 is then treated to remove the benzyl protecting group to form

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the phenol represented by Structural Formula II-7. Methods of removing a benzyl protecting group from a phenol can be found in Green, et al., Protective Groups in Organic Synthesis, 2nd edition, (1991), John Wiley & Sons, Inc., New 5 York, pages 156-158, the entire teachings of which are incorporated herein by reference. A preferred method of removing a benzyl protecting group is by treating the compound represented by Structural Formula II-3 with hydrogen in the presence of palladium on carbon (Pd-C) catalyst.

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Scheme II (continued)

In Scheme III, the 2-(oxazol-4-yl)ethyl sulfonyl ester is then reacted with a phenol represented by Structural Formula II-7 in the presence of a metal carbonate, such as cesium carbonate, to form a 2-(3-{2-[2-oxazol-4-yl]ethoxy}-2-phenoxy)-alkanoic acid ester represented by Structural Formula III-1. In Structural Formula II-7, R3, R4 and R6 are as previously defined while R20 is a C1-C4 alkyl. 10 reaction is typically carried out in a polar, aprotic solvent such as dimethylformamide at about 40°C to about 70°C and is allowed to proceed for about 10 hours to about 24 hours. The reactants (i.e., the compounds represented by Structural Formulas IA-8 and II-7) are present in about 15 equal molar amounts or with about 0.1 M to about 0.5 M excess of the sulfonyl ester compound represented by Structural Formula IA-8. The cesium carbonate is present in about one molar equivalent to about 1.5 molar equivalents with respect to the sulfonyl ester. 20

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Alternatively, the 2-(oxazol-4-yl)ethyl sulfonyl ester is reacted with a phenol represented by Structural Formula II-7 in the presence of a hindered base to form a 3-(4-{2-[2-oxazol-4-yl]ethoxy}-phenyl)-2-methyl-2-phenoxy-propanoic acid ester represented by Structural Formula III-1. The reaction is typically carried out in a polar solvent such as an alcohol at about 40°C to about 70°C and is allowed to proceed for about 24 hours to about 48 hours. The reactants (i.e., the compounds represented by Structural Formulas IA-8 and II-7) are present in about equal molar amounts. The alkaline metal carbonate is present in about 20 molar equivalents and is preferably bound to an inert solid support such as polystyrene.

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Scheme III

Hydrolysis of the $2-(3-\{2-[2-oxazol-4-yl]ethoxy\}-2$ phenoxy)-alkanoic acid ester, represented by Structural Formula III-1 wherein R20 is a C1-C4 alkyl, is typically carried out in an alcohol solvent in the presence of an excess of aqueous alkali metal hydroxide. The reaction is heated at about 50 °C to about 60 °C and is allowed to proceed for about 10 hours to about 24 hours to form a 2-(3-{2-[2-oxazol-4-y1]ethoxy}-2-phenoxy)-alkanoic acid

10 represented by Structural Formula III-1 wherein R20 is H.

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EXEMPLIFICATION

Instrumental Analysis

5 Infrared spectra were recorded on a Perkin Elmer 781 spectrometer. ¹H NMR spectra were recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s 10 = singlet, d = doublet, t = triplet, g = quartet, qn = quintet and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C NMR were recorded on a Varian 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, 15 with the solvent resonance employed as the internal standard (CDC1 $_3$ at 77.0 ppm and DMSO-d $_6$ at 39.5 ppm). Combustion analyses were performed by Eli Lilly & Company Microanalytical Laboratory. High resolution mass spectra were obtained on VG ZAB 3F or VG 70 SE spectrometers. 20 Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light.

Standard Synthesis Procedures

25 Certain standard synthesis procedures were used in preparing many of the exemplified compounds of the present invention. These standard procedures were:

Standard Procedure (A): Toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester (0.47 g, 0.132)
30 mmol) was added to a one dram, screw-cap vial and diluted with ethanol (0.5 mL). To this solution are added 3-(4-

hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester (0.5 mL of a 0.264 M solution in ethanol, 0.132 mmol) and polystyrene bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (100-125 mg, 2.6 mmol/g) and the vial was tightly closed. The reaction vessel was heated in a block heater for 24-48 h at 55 °C, or until TLC or MS analysis indicates the disappearance of starting materials. The suspension was filtered while warm and the residue washed with ethanol (1 mL). The solution was treated with aqueous NaOH (5N 10 solution, 100 μ l) and the vial resealed tightly. The solution was heated in a block heater at 55 °C for 3-16 h, or until MS analysis indicates the completion of the hydrolysis. The solvents are removed with a stream of nitrogen or under reduced pressure and the residue redissolved in 1 mL water. The solution was acidified with 15 aqueous HCl (5N solution, 150 μ l), often causing precipitation of product. The suspension was diluted with dichloromethane (3 mL) and the resultant biphasic solution was filtered through a Chrom-Elut column to remove water. 20 The filtrate was concentrated in vacuo and the resultant residue was purified by mass-directed HPLC to provide analytically pure material. Overall yield after purification 25%.

Standard Procedure (B): A mixture of 3-(4-hydroxy-phenyl)2-methyl-2-m-tolyloxy-propionic acid ethyl ester (0.095 g,
0.030 mmol), toluene-4-sulfonic acid 2-(5-methyl-2-phenyloxazol-4-yl)-ethyl ester (0.108 g, 0.030 mmol) and 325 mesh
K₂CO₃ (0.084 g, 0.60 mmol) in ethanol (2 mL) was heated to
reflux for 24 h under N₂. Aqueous 5N NaOH (0.5 mL) and
30 additional ethanol (1 mL) was added to the reaction mixture
and it was heated at reflux for an additional 2 h. The

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reaction was cooled and the solvent removed in vacuo. The residue was acidified with aqueous 1 N HCl (5 mL), extracted with water and CH₂Cl₂ and the organic layer dried by passing it through a Varian Chem Elut 1003 cartridge. The solvent was removed in vacuo to give 0.134 g of crude product which was purified by LCMS to give 0.036 g (25%) of analytically pure 2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-m-tolyloxy-propionic acid.

Exemplified Compounds

Example 1 rac-3-{4-[2-(2-Phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-

2-methyl-2-phenoxy-propionic acid

The title compound, shown above, was made as described below.

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Step A
2-Phenoxypropionic acid ethyl ester

Phenol (28.5 g, 0.30 mol), Cs_2CO_3 (197.0 g, 0.61 mol), 5 and ethyl 2-bromopropionate (54.3 g, 0.30 mol) were combined in anhydrous N, N-dimethylformamide (DMF) (1000 mL) and stirred at 90 °C under an atmosphere of nitrogen. After 16 h, the DMF was removed in vacuo. The residue was dissolved in ethyl acetate (300 mL) and washed twice with water and 10 once with brine. The organic layer was dried over Na2SO4 and concentrated in vacuo to produce 2-phenoxypropionic acid ethyl ester, shown above, as a golden oil (48.5 g, 83%) 1H NMR (250 MHz, CDCl₃): δ 7.31 (d, 2H, J=7.8), 7.02 (t, 1H, J=7.9), 6.93 (d, 2H, J=7.8), 4.79 (q, 1H, J=6.1), 4.26 (q, 15 2H, J=7.2), 1.66 (d, 3H, J=6.1), 1.24 (t, 3H, J=7.2). MS [EI+] 195 (M+H) +

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Step B

2-Phenoxy-3-(4-benzyloxyphenyl)-2-methyl-propionic acid
ethyl ester

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A solution of lithium diisopropylamide (LDA) (16.5 mL, 24.7 mmol, 1.5M in cyclohexane) was cooled to -78 °C in a dry ice/acetone bath and then added to a solution of 3-(4hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester (4.79 g, 24.7 mmol) in anhydrous tetrahydrofuran (THF) (30 mL) also cooled to -78 °C under an atmosphere of nitrogen. After 5 min, 4-benzyloxybenzaldehyde (4.76 g, 22.4 mmol) was added in one portion. After stirring for 10 min, the reaction mixture was quenched with saturated solution of aqueous NH4Cl (10 mL) and the mixture allowed to warm to ambient temperature. The biphasic mixture was diluted with ether (100 mL) and partitioned, and the organic layer was washed with brine, dried over MgSO4 and concentrated in vacuo. The residue was purified by flash column chromatography (600 g silica, 25x200 mL fractions, gradient elution 0-20% ethyl acetate in hexanes) to provide a colorless oil (3.84 g, 42%) as a mixture of inseparable diastereomers of 2-phenoxy-3-(4-benzyloxy-phenyl)-3-hydroxy-2-methylpropionic acid ethyl ester which was used without

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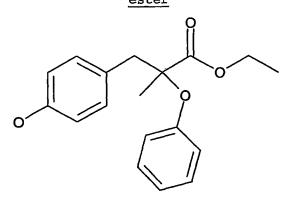
further characterization or purification. $R_f = 0.32$ in 4:1 hexanes:ethyl acetate.

2-Phenoxy-3-(4-benzyloxyphenyl)-3-hydroxy-2methylpropionic acid ethyl ester (3.84 g, 9.5 mmol) in anhydrous CH₂Cl₂ (30 mL) was cooled to 0 °C and treated with BF_3-Et_2O (1.16 mL, 9.5 mmol) and triethylsilane (1.51 mL, 9.5 mmol). The mixture was stirred for 2 h and gradually warmed to ambient temperature. Saturated aqueous Na₂CO₃ (15 mL) was added and the mixture was stirred vigorously. The solution was partitioned and the organic layer was washed 10 twice with water and brine, dried over Na2SO4, and concentrated in vacuo to produce 2-phenoxy-3-(4benzyloxyphenyl)-2-methyl-propionic acid ethyl ester, shown above, as a colorless oil (1.34 g, 36%). $R_f = 0.90$ (9:1 hexanes:ethyl acetate). ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.42 (m, 3H), 7.34 (t, 1H), 7.17-7.24 (m, 5H), 6.98 (t, 1H), 6.91 (d, 2H), 6.83 (d, 2H), 5.05 (s, 2H), 4.22 (q, 1H, J=7.1), 3.26 (d, 1H, J=13.7), 3.13 (d, 1H, J=13.7), 1.40 (s, 3H), 1.22 (t, 3H, J=7.1). MS [EI+] 408 (M+NH₄)⁺.

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Step C 3-(4-Hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester



2-Phenoxy-3-(4-benzyloxyphenyl)-2-methyl-propionic acid ethyl ester (830 mg, 2.1 mmol) was dissolved in ethyl acetate (30 mL) and treated with 5% palladium on carbon (300 mg), and then stirred under an atmosphere of hydrogen for 20 h. The suspension was filtered through celite and concentrated in vacuo to produce 3-(4-hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester colorless oil (563 mg, 89%) ¹H NMR (300 MHz, CDCl₃): δ 7.23 (t, 2H), 7.13 (d, 2H), 6.96 (t, 1H), 6.83 (d, 2H), 6.76 (d, 2H), 4.19 (q, 1H, J=7.1), 3.23 (d, 1H, J=12.4), 3.08 (d, 1H, J=12.4), 1.39 (s, 3H), 1.22 (t, J=7.1). MS [EI+] 318 (M+H)⁺, [EI-] 359

Additional 3-(4-hydroxyphenyl)-2-methyl-2phenoxypropionic acid ethyl ester(approx 48 g), prepared in
the same manner, was purified by chiral chromatography to
provided the individual enantiomers (Chiralcel OD, 8 x 27
cm, 7% IPA/heptane, 248 nm; (S)-isomer: 97.2% ee; (R)isomer: >99% ee).

 $(M+OAc^{-})$.

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Step D

3-{4-[2-(2-Phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxy-propionic acid ethyl ester

5 3-(4-Hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester (495 mg, 1.7 mmol), toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester (766 mg, 2.2 mmol) and Cs₂CO₃ (700 mg, 2.2 mmol) were combined in anhydrous DMF (25 mL) and stirred for 16 h at 55 °C under an atmosphere of nitrogen. The mixture was then cooled and 10 diluted with ethyl acetate (100 mL), and washed with water then brine. The organic layer was dried with Na2SO4 and concentrated in vacuo to a viscous yellow oil. The residue was purified by flash column chromatography (100 g silica, 60x15mL fractions, gradient elution 0-20% ethyl acetate in 15 hexanes) to provide the ethyl ester as a colorless oil (48%). ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3)$: δ 7.96 (m, 2H), 7.41 (m, 3H), 7.19 (t, 2H), 7.12 (d, 2H), 6.93 (t, 1H), 6.82 (m, 4H), 4.20 (q, 2H), 4.18 (t, 2H), 3.23 (d, 1H), 3.06 (d, 1H), 2.95 (t, 2H), 2.37 (s, 3H), 1.33 (s, 3H). MS [EI+] $486 (M+H)^{+}$, [EI-] 20 $484 (M-H)^{+}$

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Step E

3-{4-[2-(2-Phenyl-5-methyl-oxazol-4-y1)-ethoxy]-phenyl}-2 methyl-2-phenoxy-propionic acid

The title compound, was prepared as follows. 3-{4-[2-5] (2-Phenyl-5-methyl-oxazol-4-yl)ethoxy]-phenyl}-2-methyl-2-phenoxypropionic acid ethyl ester (4.6 g, 9.5 mmol) was dissolved in methanol (75 ml) and treated with 2.0 N NaOH (75 ml) with vigorous stirring, causing slight precipitation. The suspension was heated for 18 h at 55 C, allowing full dissolution of all reagents. The methanol was then removed in vacuo and the aqueous residue was acidified with 5.0 N HCl (75 ml) at 0 °C. The suspension was extracted into ethyl acetate and the orgnaic solution dried over Na₂SO₄ and concentrated to produce a white solid (94%).

15 ¹H NMR (300 MHz, d₆-DMSO): δ 7.87 (m, 2H), 7.44 (m, 3H), 7.21 (dd, 2H, J = 7.8, 8.8), 7.10 (d, 2H, J = 8.8), 6.91 (t, 1H, J = 8.8), 6.81(d, 2H, J = 7.8), 6.77 (d, 2H, J = 7.8), 4.14 (t, 2H, J = 6.6), 3.14 d, 1H, J = 12.0), 3.01 (d, 1H, J = 12.0), 2.88 (d, 2H, J = 6.6), 2.31 (s, 3H), 1.24 (s, 3H). MS [EI+] 458

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Example 2

(R)-3-{4-[2-(2-Phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-phenoxy-propionic acid

5 (R)-3-(4-hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester, shown below,

from Example 1, Step C, and toluene-4-sulfonic acid 2-(2-phenyl-5-methyloxazol-4-yl)-ethyl ester were reacted, as

10 described in Example 1, Step D, to provide (R)-3-{4-[2-(2-phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxypropionic acid ethyl ester, shown below, as a colorless oil (61%). ¹H NMR (300 MHz, CDCl₃): δ 7.96 (m, 2H), 7.41 (m, 3H), 7.19 (t, 2H), 7.12 (d, 2H), 6.93 (t, 1H), 6.82 (m, 4H), 4.20 (q, 2H), 4.18 (t, 2H), 3.23 (d, 1H), 3.06 (d, 1H), 2.95 (t, 2H), 2.37 (s, 3H), 1.33 (s, 3H). MS [EI+] 486 (M+H)⁺, [EI-] 484 (M-H)⁺.

The title compound was then prepared from this phenoxy propionic acid ethyl ester, via the hydrolysis procedure of Example 1, Step E, to produce a white solid (99%). ¹H NMR

5 (300 MHz, d₆-DMSO): δ 7.87 (m, 2H), 7.44 (m, 3H), 7.21 (dd, 2H, J=7.8, 8.8), 7.10 (d, 2H, J=8.8), 6.91 (t, 1H, J=8.8), 6.81(d, 2H, J=7.8), 6.77 (d, 2H, J=7.8), 4.14 (t, 2H, J=6.6), 3.14 d, 1H, J=12.0), 3.01 (d, 1H, J=12.0), 2.88 (d, 2H, J=6.6), 2.31 (s, 3H), 1.24 (s, 3H). MS [EI+] 458

10 (M+H)⁺, [EI-] 456 (M-H)⁺.

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Example 3

(S)-3-{4-[2-(2-Phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-phenoxy-propionic acid

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(S)-3-(4-hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester, shown below,

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from Example 1, Step C, and toluene-4-sulfonic acid 2-(2-phenyl-5-methyloxazol-4-yl)-ethyl ester were reacted, as described in Example 1, Step D, to provide (S)-3-{4-[2-(2-phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxypropionic acid ethyl ester, shown below, as a colorless oil (41%). ¹H NMR (300 MHz, CDCl₃): δ 7.96 (m, 2H), 7.41 (m, 3H), 7.19 (t, 2H), 7.12 (d, 2H), 6.93 (t, 1H), 6.82 (m, 4H), 4.20 (q, 2H), 4.18 (t, 2H), 3.23 (d, 1H), 3.06 (d,

1H), 2.95 (t, 2H), 2.37 (s, 3H), 1.33 (s, 3H). MS [EI+] 486 $(M+H)^+$, [EI-] 484 $(M-H)^+$.

The title compound was then prepared from this phenoxy propionic acid ethyl ester, via the hydrolysis procedure of Example 1, Step E, to produce a white solid (96%). ¹H NMR (300 MHz, d_6 -DMSO): δ 7.87 (m, 2H), 7.44 (m, 3H), 7.21 (dd, 2H, J =7.8, 8.8), 7.10 (d, 2H, J =8.8), 6.91 (t, 1H, J =8.8), 6.81(d, 2H, J =7.8), 6.77 (d, 2H, J = 7.8), 4.14 (t, 10 2H, J =6.6), 3.14 d, 1H, J =12.0), 3.01 (d, 1H, J =12.0), 2.88 (d, 2H, J =6.6), 2.31 (s, 3H), 1.24 (s, 3H). MS [EI+] 458 (M+H)⁺, [EI-] 456 (M-H)⁺.

Example 4

5 <u>rac-2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-</u> ethoxy]-phenyl}-2-phenoxypropionic acid

3-(4-Hydroxyphenyl)-2-methyl-2-phenoxypropionic acid 10 ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2thiophen-2-yl-oxazol-4-yl)-ethyl ester, shown below,

were reacted, as described in Example 1, Step D, to provide 2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxypropionic acid ethyl ester, shown below, as a colorless oil (30%). ¹H NMR (300 MHz, CDCl₃): δ 7.59 (d, 1H), 7.37 (d, 1H), 7.24 (t, 2H), 7.13, (d, 2H), 7.09 (t, 1H), 6.96 (t, 1H), 6.83 (d, 2H), 6.82 (d, 2H), 4.21 (t, 2H), 4.19 (q, 2H), 3.26 (d, 1H), 3.12 (d, 1H), 2.95 (t,

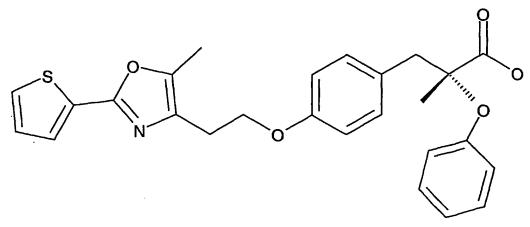
2H), 2.35 (s, 3H), 1.39 (s, 3H), 1.21 (t, 3H). MS [EI+] 492 $(M+H)^+$, [EI-] 490 $(M-H)^+$

The title compound was then prepared from this phenoxy propionic acid ethyl ester, using the hydrolysis procedure of Example 1, Step E, to provide a white solid (88%). ¹H NMR (300 MHz, d_6 -DMSO): δ 7.70 (d, 1H, J =5.1), 7.57 (d, 1H, J =3.5), 7.23 (t, 2H, J =7.4), 7.15 (dd, 1H, J =3.5,5.1), 7.12 (d, 2H, J =8.6), 6.93 (dd, 1H, J =7.4, 7.8), 6.83 (d, 2H, J =8.6), 6.79 (d, 2H, J =7.8), 4.14 (t, 2H, J =6.6), 3.15 (d, 1H, J =13.7), 3.03 (d, 1H, J =13.7), 2.87 (t, 2H, J =6.6), 2.30 (s, 3H), 1.26 (s, 3H). MS [EI+] 464 (M+H)⁺, [EI-] 462 (M-H)⁺ HPLC: T= 2.78 min, purity 99%.

Example 5

15

(R)-2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxypropionic acid



(R)-3-(4-Hydroxyphenyl)-2-methyl-2-phenoxypropionic

acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester were reacted, as described in Example 1, Step D, to provide (R)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]- phenyl}-2-phenoxypropionic acid ethyl ester, shown below, as a colorless oil (54%). ¹H NMR (300 MHz, CDCl₃): δ 7.59 (d, 1H), 7.37 (d, 1H), 7.24 (t, 2H), 7.13, (d, 2H), 7.09 (t, 1H), 6.96 (t, 1H), 6.83 (d, 2H), 6.82 (d, 2H), 4.21 (t, 2H), 4.19 (q, 2H), 3.26 (d, 1H), 3.12 (d, 1H), 2.95 (t, 2H), 2.35 (s, 3H), 1.39 (s, 3H), 1.21 (t, 3H). MS [EI+] 492 (M+H)⁺, [EI-] 490 (M-H)⁺.

The title compound was then prepared using the

15 hydrolysis procedure of Example 1, Step E, to provide a

white solid (78%). ¹H NMR (300 MHz, d₆-DMSO): • 7.70 (d, 1H,

J=5.1), 7.57 (d, 1H, J=3.5), 7.23 (t, 2H, J=7.4), 7.15

(dd, 1H, J=3.5,5.1), 7.12 (d, 2H, J=8.6), 6.93 (dd, 1H, J

=7.4, 7.8), 6.83 (d, 2H, J=8.6), 6.79 (d, 2H, J=7.8), 4.14

20 (t, 2H, J=6.6), 3.15 (d, 1H, J=13.7), 3.03 (d, 1H, J

=13.7), 2.87 (t, 2H, J=6.6), 2.30 (s, 3H), 1.26 (s, 3H). MS

[EI+] 464 (M+H)⁺, [EI-] 462 (M-H)⁺.

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Example 6 (S)-2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-

ethoxy]-phenyl}-2-phenoxypropionic acid

(S)-3-(4-hydro

5

(S)-3-(4-hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester were reacted, as described in Example 1, Step D, to provide (S)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxypropionic acid ethyl ester, shown below, as a colorless oil (48%). ¹H NMR (300 MHz, CDCl₃): δ 7.59 (d, 1H), 7.37 (d, 1H), 7.24 (t, 2H), 7.13, (d, 2H), 7.09 (t, 1H), 6.96 (t, 1H), 6.83 (d, 2H), 6.82 (d, 2H), 4.21 (t, 2H), 4.19 (q, 2H), 3.26 (d, 1H), 3.12 (d, 1H), 2.95 (t, 2H), 2.35 (s, 3H), 1.39 (s, 3H), 1.21 (t, 3H). MS [EI+] 492 (M+H)⁺, [EI-] 490 (M-H)⁺.

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The title compound was then prepared using the hydrolysis procedure of Example 1, Step E, to provide a white solid (78%). ¹H NMR (300 MHz, d₆-DMSO): δ 7.70 (d, 1H, J =5.1), 7.57 (d, 1H, J =3.5), 7.23 (t, 2H, J =7.4), 7.15 (dd, 1H, J =3.5,5.1), 7.12 (d, 2H, J =8.6), 6.93 (dd, 1H, J =7.4, 7.8), 6.83 (d, 2H, J =8.6), 6.79 (d, 2H, J =7.8), 4.14 (t, 2H, J =6.6), 3.15 (d, 1H, J =13.7), 3.03 (d, 1H, J =13.7), 2.87 (t, 2H, J =6.6), 2.30 (s, 3H), 1.26 (s, 3H). MS [EI+] 464 (M+H)⁺, [EI-] 462 (M-H)⁺.

Example 7

2-Methyl-3-(4-{2-[5-methyl-2-cyclohexyl-oxazol-4-yl]ethoxy}-phenyl)-2-phenoxypropionic acid

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The title compound, shown above, was synthesized as follows:

Step A

20 <u>2-(Cyclohexanecarbonyl-amino)-succinic acid 4-benzyl ester</u>

Benzyl L-aspartate (25.0 g, 0.109 moles), DI water (325 mL), acetone (25 mL), and Na₂CO₃ (41.1 g, 0.384 mol) were

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combined and cooled to 8 °C. Cyclohexanecarbonyl chloride (16 mL, 0.120 mol) was added dropwise via addition funnel over 10 min. The reaction was allowed to warm to ambient temperature and stirred for at least 90 min. Concentrated 5 HCl (50 mL) was added to the slurry until the pH was ≤ 4.0 The mixture was stirred for an additional 45 min, and then filtered. The solid was rinsed with DI water (2x 25 mL) and dried under vacuum at 30 °C overnight to provide 34.3 g of crude amide. Further purification was not necessary.

Step B

10

3-(Cyclohexanecarbonyl-amino)-4-oxo-pentanoic acid benzyl ester

15 In a 2L flask, 2-(cyclohexanecarbonyl-amino)-succinic acid 4-benzyl ester (34.2 g, 0.102 moles), pyridine (155 mL) and acetic anhydride (127 mL) were combined. The reaction mixture was heated to 90 °C for 2 h and then cooled to ambient temperature. DI water (950 mL) was added slowly and the reaction mixture cooled to ambient temperature before 20 adding conc. HCl (50 mL) to the slurry until the pH was \leq 4.0 (pH paper). After stirring for 45 min, the solid was filtered, rinsed with DI water (2x 50 mL) and then dried under vacuum at 40 °C overnight to obtain 26.0 g of crude 25 ketone. Further purification was not necessary.

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Step C

(2-Cyclohexyl-5-methyl-oxazol-4-yl)-acetic acid benzyl ester

Phosphorous oxychloride (22 mL, 0.235 moles, 3.0 eq) was added dropwise to a solution of 3-(cyclohexanecarbonylamino)-4-oxo-pentanoic acid benzyl ester (26.0 g, 0.078 moles) in DMF (330 mL). The mixture was heated to 90 °C for 30 min, and then cooled to ambient temperature before diluting by slowly adding DI water (600 mL, Caution, exothermic). The mixture was cooled to ambient temperature and extracted with MTBE (3x 150 mL). The combined organic phases were washed with DI water, brine (150 mL), dried over MgSO4 and concentrated to obtain 21.1 g as a brown oil. Further purification was not necessary.

15 Step D

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(2-Cyclohexyl-5-methyl-oxazol-4-yl)-acetic acid benzyl

(2-Cyclohexyl-5-methyl-oxazol-4-yl)-acetic acid

ester (23.8 g , 0.076 moles), 2B-3 ethanol (120 mL), DI water (95 mL) and KOH (10.0 g, 0.152 moles, 2 eq) were stirred at ambient temperature for 60 min or until HPLC showed disappearance of benzyl ester. The reaction mixture was concentrated and then conc. HCL was added to the oily residue until the pH = 1 (pH paper). The reaction mixture was partitioned with MTBE (100 mL) and then the organic layer was washed with DI water, brine (1x 120 mL), dried over MgSO₄ and concentrated to obtain a brown semi-solid.

The brown semi-solid was dissolved in 5 % Na₂CO₃ (100 mL) and washed with MTBE (3x 100 mL). The combined organic phases were back-extracted with 5 % Na₂CO₃ (1x 50 mL). combined aqueous layers were acidified to pH=1 with conc. HCl and extracted with MTBE (3x 50 mL). The combined

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organic phases were washed with brine (1x 50 mL), dried over MgSO $_4$ and concentrated to obtain 9.5 g of acid. The 1 H NMR showed < 1 % benzyl alcohol.

Step E

5

2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethanol

BH3-THF complex (96 mL, 0.096 moles, 2.3 eq) was added dropwise via addition funnel to a solution of (2-cyclohexyl-10 5-methyl-oxazol-4-yl)-acetic acid (9.4 g, 0.041 moles) in THF (45 mL) over 50 min. The reaction mixture was stirred for 3 h, and then quenched with MeOH (30 mL). After heating at 60 °C for 2 h, the reaction mixture was cooled to ambient temperature, concentrated and the residue dissolved in CH_2Cl_2 (50 mL). The organic phase was washed with 1N NaOH 15 and brine (1x 50 mL), dried over MgSO4 and concentrated to obtain 7.80 g of a yellow oil. The 1H NMR was consistent with desired product. ¹H NMR (400 MHz, CDCl₃) $\delta 3.73$ (t, J =6.8 Hz, 2H), 2.58 (tt, J = 11.6, 3.6 Hz, 1H), 2.54 (t, J =20 6.8 Hz, 2H), 2.13 (s, 3H), 1.93-1.89 (m, 2H), 1.74 (dt, J =12.8, 3.6 Hz, 2H), 1.67-1.62 (m, 1H), 1.41 (qd, J = 12.0, 3.2 Hz, 1H), 1.33-1.17 (m, 4H); MS (EI+) 210.1 (M+H), 232.1 (M+H+Na).

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Step F

Toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester

5 A solution of 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)ethanol, (8.7 g, 41.6 mmol) in CH_2Cl_2 (120 mL) at ambient temperature was treated with pyridine (12 mL, 150 mmol), 4dimethylamino pyridine (DMAP) (1.6 g, 13.1 mmol), and tosyl anhyride (25.3 g, 77.5 mmol). After 18 h, the reaction 10 mixture was partitioned with vigorous stirring between CH2Cl2 and 1N HCl. The aqueous layer was extracted with CH_2Cl_2 and then combined organic phases were washed with brine, dried (MgSO4), filtered and concentrated. The residue was purified by Biotage chromatography (40 L, 25% EtOAc/hexanes) to provide the product (9.8 g, 65%): ¹H NMR 15 $(400 \text{ MHz}, \text{CDCl}_3) \delta 7.67 (d, J = 8.4 \text{ Hz}, 2\text{H}), 7.27 (d, J = 8.4)$ Hz, 2H), 4.16 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.56 (tt, J = 11.6, 3.6 Hz, 1H), 2.39 (s, 3H), 2.13 (s, 3H), 1.93-1.89 (m, 2H), 1.74 (dt, J = 12.8, 3.6 Hz, 2H), 1.67-1.62 (m, 1H), 1.41 (qd, J = 12.0, 3.2 Hz, 1H), 1.33-1.17 (m, 20 4H); MS (EI+) 364.1 (M+H).

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Step G

2-Methyl-3-(4-{2-{5-methyl-2-cyclohexyl-oxazol-4-yl}ethoxy}-phenyl)-2-phenoxypropionic acid ethyl ester

3-(4-Hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester (300 mg, 1.0 mmol), toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester (386 mg, 1.06 mmol) and Cs₂CO₃ (423 mg, 1.3 mmol) were combined in anhydrous DMF (7 mL) and stirred for 16 h at 55 °C under an atmosphere of nitrogen. The mixture was then cooled, diluted with ethyl acetate (50 mL), and washed with water and brine. The organic layer was dried with Na₂SO₄ and concentrated in vacuo to a viscous yellow oil. The residue was purified by flash column chromatography (100 g silica, 60x15mL) fractions, gradient elution 0-20% ethyl acetate in hexanes) to provide the ethyl ether compound as a colorless oil (177

Step H

20 <u>2-Methyl-3-(4-{2-[5-methyl-2-cyclohexyl-oxazol-4-yl]-</u> <u>ethoxy}-phenyl)-2-phenoxypropionic acid</u>

mg, 28%).

The title compound was produced as follows.

2-Methyl-3-(4-{2-[5-methyl-2-cyclohexyl-oxazol-4-yl]-ethoxy}-phenyl)-2-phenoxypropionic acid ethyl ester (175 mg, 3.6 mmol) in MeOH (7 mL) was treated with 2N NaOH (7 mL) and warmed to 55 °C. After 18 h, the mixture was concentrated

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under reduced pressure and then acidified with 5N HCl to a pH of 1. The solution was extracted with EtOAc and then the organic phases dried (Na₂SO₄), filtered and concentrated to a white foam (157 mg, 88%): ¹H NMR (300 MHz, d₆-DMSO): δ7.23

5 (t, J = 7.2 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 6.91 (dd, J = 7.3, 7.2 Hz, 1H), 6.82 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 7.3 Hz, 2H), 4.16 (t, J = 6.3 Hz, 2H), 3.14 (d, J = 14.0 Hz, 1H), 3.02 (d, J = 14.0 Hz, 1H), 2.77 (t, J = 6.3 Hz, 2H), 2.66 (m, 1H), 2.18 (s, 3H), 1.90 (m, 1H), 1.86 (m, 1H), 1.69

10 (m, 2H), 1.61 (m, 1H), 1.42 (m, 2H), 1.27 (m, 1H), 1.24 (s, 3H), 1.21 (m, 2H). MS [EI+] 464 (M+H)⁺, [EI-] 462 (M-H)⁺. HPLC: T= 2.98 min, purity 94%.

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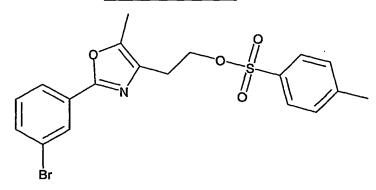
Example 8

3-(4-{2-[2-(3-Bromopheny1)-5-methyloxazo1-4-y1]ethoxy}pheny1)-2-methyl-2-phenoxypropionic acid

Step A

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Toluene-4-sulfonic acid 2-[2-(3-bromopheny1)-5-methyloxazol-4-yl]ethyl ester



10 To a solution of 2-(3-bromophenyl)-5-methyl-4-oxazole ethanol (3.27 g, 11.6 mmol) in CH₂Cl₂ (46 mL) at rt under N₂ was added pyridine (3.28 mL) and DMAP (0.43 g, 3.48 mmol) followed by portionwise addition of tosyl anhydride (4.54 g, 13.9 mmol). The reaction exothermed to 32 °C and was stirred 2 h before 1N HCl (50 mL) was added. The mixture was stirred vigorously 15 min, and then the organic phase was dried (MgSO₄) and then concentrated under reduced pressure. The residue was purified by column chromatography

(40 mL SiO₂, 50% EtOAc/hexanes) to provide toluene-4-sulfonic acid 2-[2-(3-bromophenyl)-5-methyloxazol-4-yl]ethyl ester (4.58 g, 91%) as a white powder: 1 H NMR (400 MHz, CDCl₃) δ 8.01 (t, J = 1.6 Hz, 1H) 7.80 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.53 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 4.30 (t, J = 6.4 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H); MS (EI) 437.0 (M + H)⁺.

10 Step B

3-(4-{2-[2-(3-Bromopheny1)-5-methyloxazol-4-y1]ethoxy}pheny1)-2-methyl-2-phenoxypropionic acid ethylester

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This compound was prepared according to the procedure in Example 1, part D, using 3-(4-hydroxyphenyl)-2-methyl-2-phenoxy-propionic acid ethyl ester (551.5 mg, 1.84 mmol) and toluene-4-sulfonic acid 2-[2-(3-bromophenyl)-5-methyloxazol-4-yl]ethyl ester (1.04g, 2.39 mmol): Rf = 0.54 in 1:4 EtOAc:hexanes; ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H) 7.30 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.98-6.95 (m, 1H), 6.82 (d, J = 8.4 Hz, 2H) 6.83-6.81 (m, 2H), 4.23 (t, J = 6.8 Hz, 2H), 4.20 (q, J = 7.6 Hz, 2H), 3.26 (d, J = 14.0 Hz, 1H), 3.09 (d, J = 14.0 Hz, 1H),

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2.97 (t, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.38 (s, 3H),1.21 (t, J = 7.6 Hz, 3H); MS (EI) = 564.2 (M + H)⁺.

Step C

3-(4-{2-[2-(3-Bromopheny1)-5-methyloxazol-4-yl]ethoxy}pheny1)-2-methyl-2-phenoxypropionic acid

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The title compound was prepared according to the procedure in Example 1, Step E, using $3-(4-\{2-[2-(3-bromopheny1)-5-methyloxazol-4-y1]ethoxy\}pheny1)-2-methyl-2-phenoxypropionic acid ethyl ester (52 mg, 0.092 mmol): <math>^1H$ NMR (400 MHz, DMSO-d₆) δ 7.96 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.91 (t, J = 7.6 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.89 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 4.12 (t, J = 6.8 Hz, 2H), 3.11 (d, J = 13.6 Hz, 1H), 2.99 (d, J = 13.6 Hz, 1H), 2.86 (t, J = 6.8 Hz, 2H), 2.30 (s, 3H), 1.21 (s, 3H); MS (EI) 536.1 (M + H)⁺, 535.1 (M - H)⁻.

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Example 9

2-Methyl-3-(4-{2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl]ethoxy)phenyl)-2-phenoxypropionic acid

In this synthesis, the following chemical intermediates and title compound were sequentially formed by the procedure of Example 7 using 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl]ethanol, shown below.

Toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl]ethyl ester, shown below:

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¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 8.4 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 2.76 (t, J = 6.6 Hz, 2H), 2.42 (s, 3H), 2.17 (s, 3H), 2.61-2.02 (m, 2H), 1.56-1.30 (m, 8H), 1.19 (s, 3H); MS (EI) 378.2 (M + H)⁺.

2-Methyl-3-(4-{2-[5-methyl-2-(1-methylcyclohexyl) oxazol-4-yl]ethoxy}phenyl)-2-phenoxypropionic acid ethyl ester, shown below:

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10 ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.19 (m, 2H), 7.15-7.13 (m, 2H), 6.99-6.95 (m, 1H), 6.83-6.80 (m, 4H), 4.20 (q, J = 7.6 Hz, 2H), 4.14 (t, J = 6.4 Hz, 2H), 3.29 (d, J = 14.0 Hz, 1H), 3.10 (d, J = 14.0 Hz, 1H), 2.89 (t, J = 6.4 Hz, 2H), 2.24 (s, 3H), 2.11 (broad m, 2H), 1.56-1.24 (v. broad m, 14H), 1.21 (t, J = 7.6 Hz, 3H); MS (EI) 506.3 (M + H)⁺, 528.3 (M + Na)⁺.

The title compound, 2-methyl-3-(4-{2-[5-methyl-2-(1-methylcyclohexyl) oxazol-4-yl]ethoxy}phenyl)-2-phenoxypropionic acid: ¹H NMR (400 MHz, DMSO-d₆) δ 7.24 (t, J = 7.2

Hz, 2H), 7.12 (d, J = 8.4Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H),
6.81 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 7.2 Hz, 2H), 4.09 (t,
J = 6.8 Hz, 2H), 3.16 (d, J = 13.2 Hz, 1H), 3.03 (d, J =
13.2 Hz, 1H), 2.78 (t, J = 6.8 Hz, 2H), 2.19 (s, 3H), 2.031.99 (m, 2H), 1.48-1.27 (m, 11H), 1.16 (s, 3H); MS (EI)

478.3 (M + H)⁺, 476.3 (M - H)⁻.

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Example 10

3-{4-[2-(2-Cyclohex-1-enyl-5-methyloxazol-4-y1)ethoxy]phenyl}-2-methyl-2-phenoxypropionic acid

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In this synthesis, the following chemical intermediates and the title compound were sequentially prepared by the procedure of Example 7 using 2-(2-cyclohex-1-enyl-5-methyl-oxazol-4-yl)ethanol, shown below.

Toluene-4-sulfonic acid 2-(2-cyclohex-1-enyl-5-methyloxazol-4-yl)ethyl ester, shown below: 1 H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.61 (s, 1H), 4.23 (t, J = 6.4 Hz, 2H) 2.76 (t, J = 6.4 Hz, 2H), 2.42-2.20 (m, 8H), 1.72-1.63 (m, 6H); MS (EI) 362.2 (M + H)⁺.

3-{4-[2-(2-Cyclohex-1-enyl-5-methyloxazol-4-yl)ethoxy] phenyl}-2-methyl-2-phenoxypropionic acid ethyl ester, shown 5 below:

¹H NMR (400 MHz, CDCl₃) δ 7.23-7.19 (m, 2H), 7.15-7.13 (m, 2H), 6.97 (m, 1H), 6.83-6.79 (m, 4H), 6.34 (s, 1H), 4.20 (q, J = 7.6 Hz, 2H, 4.16 (t, J = 6.8 Hz, 2H), 3.26 (d, J = 13.6)Hz, 1H), 3.09 (d, J = 7.6 Hz, 1H), 2.90 (t, J = 6.8 Hz, 2H), 2.45-2.43 (m, 2H), 2.28 (s, 3H), 2.22-2.21 (m, 2H), 2.04 (s, 3H), 1.73-1.64 (m, 4H), 1.38 (s, 3H), 1.26 (t, J = 7.6 Hz, 3H); MS (EI) $490.3 (M + H)^{+}$, $512.3 (M + Na)^{+}$.

The title compound, 3-{4-[2-(2-Cyclohex-1-enyl-5-15 methyloxazol-4-yl)ethoxy]phenyl}-2-methyl-2-phenoxypropionic acid: ¹H NMR (400 MHz, DMSO-d₆) δ 7.24 (t, J = 7.2 Hz, 2H), $7.12 \text{ (d, J = 8.4 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 6.82 (d,$ J = 7.2 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.55 (s, 1H),4.09 (t, J = 6.8 Hz, 2H), 3.16 (d, J = 13.2 Hz, 1H), 3.0420

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(d, J = 13.2 Hz, 1H), 2.80 (t, J = 6.8 Hz, 2H), 2.32 (bs, 2H) 2.23 (s, 3H), 2.16-2.15 (m, 2H), 1.63-1.55 (m, 4H), 1.27 (s, 3H); MS (EI) 462.2 (M + H)⁺, 460.3 (M - H)⁻.

Example 11

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3-{3-Methoxy-4-[2-(5-methyl-2-thiophen-2-yloxazol-4-yl)ethoxy]phenyl}-2-methyl-2-phenoxypropionic acid

Step A

3-(4-Benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methyl-2phenoxypropionic acid

A stirred solution of LDA in cyclohexane (1.5 M) was cooled to - 20 °C, to which a solution of 2-phenoxypropionic acid (10 g, 60.2 mmol) in THF (80.3 mL) was slowly added, keeping the temperature below -10 °C. The resulting dianion solution was stirred for 15 min, then a solution of 4-benzyloxy-3-methoxybenzaldehyde (14.58 g, 60.2 mmol) in THF (80.3 mL) was added over 1 h, maintaining temperature below - 10 °C. Fifteen minutes after completion of aldehyde addition, the reaction mixture was poured onto ice water (200 mL), and extracted using 1:2 Et₂0:hexane (500 mL). The aqueous layer was isolated, extracted again with 1:2 Et₂0:hexane (240 mL), then acidified with concentrated HCl until pH = 3. The product acid was extracted into EtOAc (2 x 165 mL), which was dried over Na₂SO₄ and concentrated to

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an orange paste (16.5 g crude, 67%): MS (EI) 426.2 (M + NH_4)⁺, 407.2 (M - H)⁻.

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Step B

3-(4-Benzyloxy-3-methoxyphenyl)-2-methyl-2phenoxypropionic acid

A stirred solution of Et₃SiH (8.67 mL, 54.3 mmol) in CH_2Cl_2 (45 mL) was treated with $BF_3 \cdot Et_2O$ (6.8 mL, 54.3 mmol). 3-(4-Benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methyl-2phenoxypropionic acid (7.39g, 18.1 mmol) in CH₂Cl₂ (90.5 mL) was then added dropwise via addition funnel, maintaining temperature below -7 °C. After the addition was complete, the reaction was stirred for 1.5 h at -10 °C, then quenched 15 with 1 M NaOH (18.1 mL) and diluted with H_2O (12 mL). HCl was used to adjust pH to 4, followed by separation of layers. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL), and combined organic layers were washed first with 1N HCl (15 mL), then H_2O (15 mL), followed by drying over Na_2SO_4 20 and concentration to a gummy orange solid (6.86 g, 97%): MS (EI) 410.2 (M + NH₄)⁺, 391.3 (M - H)⁻.

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Step C 3-(4-Hydroxy-3-methoxy-pheny1)-2-methy1-2phenoxypropionic acid

A solution of 3-(4-benzyloxy-3-methoxyphenyl)-2-methyl-2-phenoxypropionic acid (6.86 g, 17.5 mmol) in EtOH (175 mL) was added to 5% Pd/C (186 mg, 10 wt %). The mixture was purged first with nitrogen, then with H₂, which was then applied at 45 p.s.i. for 2 h. Pd/C was subsequently filtered off through celite, and the filtrate was concentrated to a crude oil (5.42 g, in excess of theory). MS (EI) 301.2 (M - H)⁻.

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3-(4-Hydroxy-3-methoxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester

Step D

5 A solution of 3-(4-hydroxy-3-methoxyphenyl)-2-methyl-2phenoxy-propionic acid (4.56 g, 15.08 mmol) in EtOH (150 mL) was treated with SOCl2 and heated at 75 °C for 14 h, then cooled to rt and partitioned between EtOAc (300 mL) and H₂O (400 mL). The aqueous layer was removed and backextracted with EtOAc (100 mL). Combined organic phases were 10 washed with 10% Na₂CO₃, which was isolated and backextracted with EtOAc (100 mL). Combined organic phases were washed with brine (200 mL), dried over Na₂SO₄, concentrated, and purified by column chromatography (200 g SiO2, 1:4 EtOAc: hexanes) to provide a colorless oil, which developed a 15 green color over a 24-hour period. The material was taken up in EtOAc and filtered through celite, then concentrated to yield a colorless oil (1.99 g, 40 %): Rf=0.40 in 1:4 EtOAc:hexanes; 1 H NMR (400 MHz, CDCl₃) δ 7.66-7.55(m, 1H), 7.25-7.21 (m, 2H), 6.99-6.92 (m, 1H) 6.84-6.79 (m, 3H), 20 6.74-6.71 (m, 1H), 5.54 (s, 1H), 4.22 (q, J = 6.8 Hz, 2H), 3.84 (s, 3H), 3.30 (d, J = 14 Hz, 1H), 3.07 (d, J = 14 Hz, 1H), 1.40 (s, 3H), 1.23 (t, J = 6.8 Hz, 3H).

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Step E

3-{3-methoxy-4-[2-(5-methyl-2thiophen-2-yl-oxazol-4-yl)ethoxy]phenyl-2-methyl-2-phenoxypropionic acid

The title compound was prepared from 2-(5-methyl-2-

thiophen-2-yloxazol-4-yl)ethyl tosylate and 3-(4-hydroxy-3-methoxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester according to the parallel synthesis procedure (A). MS (EI) 494.4 (M + H)⁺.

10 Example 12

3-{4-[2-(2-Cyclohexy1-5-methyloxazol-4-yl)ethoxy]-3-methoxyphenyl}-2-methyl-2-phenoxypropionic acid

The title compound was prepared by Standard Procedure

(A), using 2-(2-cyclohexyl-5-methyloxazol-4-yl)ethyl
tosylate. MS (EI) 494.0 (M + H)⁺.

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Example 13

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3propyl-phenyl}-2-phenoxy-propionic acid ethyl ester

Step A

3-(4-Allyloxyphenyl)-2-methyl-2-phenoxy-propionic acid ethyl ester

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A solution of 3-(4-hydroxyphenyl)-2-methyl-2-phenoxy-propionic acid ethyl ester (500 mg, 1.67 mmol) in methyl ethyl ketone (6 mL) was treated with allyl bromide (232 mg, 1.92 mmol, 0.17 mL) and potassium carbonate (311 mg, 2.25 mmol) and then heated to reflux. After 18 h, the mixture was cooled to ambient temperature and then partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and then the organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (100 mL SiO₂,

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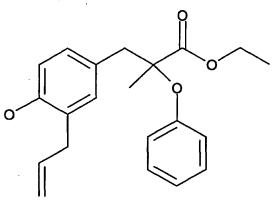
hexanes to 10% EtOAc/hexanes) to provide the desired product (478 mg, 84%) as a clear, colorless oil: 1 H NMR (400 MHz, CDCl₃) δ 7.22 (t, J = 8.0 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.97 (dt, J = 7.6, 1.2 Hz, 1H), 6.83 (d, J = 7.8 Hz, 2H), 6.84 (t, J = 8.4 Hz, 2H), 6.05 (ddd, J = 17.2, 10.6, 5.2 Hz, 1H), 5.41 (dd, J = 17.2, 1.6 Hz, 1H), 5.28 (dd, J = 10.8, 1.4 Hz, 1H), 4.22 (d, J = 5.2 Hz, 2H), 4.19 (q, J = 6.8 Hz, 2H), 3.27 (A of AB, J = 14 Hz, 1H), 3.11 (B of AB, J = 14 Hz, 1H), 1.40 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H).

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Step B

3-(3-Allyl-4-hydroxyphenyl)-2-methyl-2-phenoxy-propionic

acid ethyl ester



A solution of 3-(4-allyloxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester (475 mg, 1.39 mmol) in
dimethylaniline (1.5 mL) was heated at reflux for 18 h.
After cooling to ambient temperature, the reaction mixture
was partitioned between EtOAc and 1N H₂SO₄. The organic
phase was dried (MgSO₄), filtered and concentrated. The
residue was purified by column chromatography (100 mL SiO₂,
hexanes to 30% EtOAc/hexanes) to provide the desired product
(343 mg, 72%) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ
7.23 (t, J = 8.4 Hz, 2H), 7.02-6.96 (m, 3H), 6.83 (d, J =

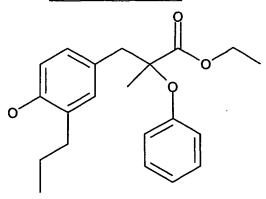
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8.8 Hz, 2H), 6.72 (d, J = 7.6 Hz, 1H), 6.05 (m, 1H), 5.16-5.09 (m, 2H), 4.21 (q, J = 6.8 Hz, 2H), 3.38 (d, J = 6.4 Hz, 2H), 3.25 (A of AB, J = 13.6 Hz, 1H), 3.10 (B of AB, J = 13.6 Hz, 1H), 1.41 (s, 3H), 1.23 (t, J = 6.8 Hz, 3H).

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Step C

3-(4-Hydroxy-3-propylphenyl)-2-methyl-2-phenoxy-propionic acid ethyl ester



10 A solution of 3-(3-allyl-4-hydroxyphenyl)-2-methyl-2phenoxy-propionic acid ethyl ester(330 mg, 0.97 mmol) in absolute EtOH (5 mL) was treated with 5% Pd/C and then the mixture was evacuated three times with N2. The reaction mixture was hydrogenated at 1 atm with an H2-filled balloon for 24 h before filtering the mixture over celite and 15 rinsing with EtOH. The product was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.22 (t, J = 7.6 Hz, 2H), 7.99-6.95 (m, 3H), 6.82 (m, 2H), 6.68 (d, J = 8.0 Hz, 1H), 4.20 (q, J = 6.8 Hz, 2H), 3.24 (A of AB, J = 13.6 Hz, 1H), 3.08 (B of AB, J = 13.6 Hz, 1H), 2.55 (t, J = 7.6 Hz, 20 2h), 1.62 (sextet, $J = 7.6 \, Hz$, 2H), 1.41 (s, 3H), 1.23 (t, J= 6.8 Hz, 3H, 0.96 (t, J = 7.2 Hz, 3H).

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Step D

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3propyl-phenyl}-2-phenoxy-propionic acid ethyl ester

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A solution of 3-(4-hydroxy-3-propylphenyl)-2-methyl-2-phenoxy-propionic acid ethyl ester (266 mg, 1.0 mmol) in DMF (10 mL) was treated with cesium carbonate (407 mg, 1.25 mmol) and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester and then heated at 55 °C for 18 h. After cooling to ambient temperature, the mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and then the organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (100 mL SiO₂, hexanes to 30% EtOAc/hexanes) to provide the desired product (315 mg, 60%) as a clear, colorless oil: MS (EI) 528.3 (M + H) $^+$.

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Step E

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-3propyl-phenyl}-2-phenoxy-propionic acid

A solution of $3-\{4-[2-(5-methyl-2-phenyloxazol-4-yl)-$ 5 ethoxy]-3-propyl-phenyl}-2-methyl-2-phenoxy-propionic acid ethyl ester in EtOH (1.5 mL) was treated with 5 N NaOH (140 μL) and then warmed to 65 °C. After 18 h, the mixture was acidified to pH = 1 with 5 N HCl. The mixture was extracted with EtOAc and then the combined organic phases were dried (MgSO₄), filtered and concentrated under reduced pressure to yield the title product. MS (EI) 500.2 (M + H)+; LC RT = 3.22 min (>99% pure).

Example 14

3-(4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-3-15 propyl-phenyl}-2-methyl-2-phenoxy-propionic acid

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The title compound, and its corresponding ester: MS (EI) 534.3 (M + H) + shown below, were synthesized according to the procedure of Example 13, Steps D and E, respectively from toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyloxazol-4-yl)-ethyl ester, and then purified by LC/MS: MS (EI) $506.2 (M + H)^+$; LC RT = 3.11 min (>85% pure).

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Example 15

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-3-propyl-phenyl}-2-phenoxy-propionic acid

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The title compound, and its corresponding ester: MS

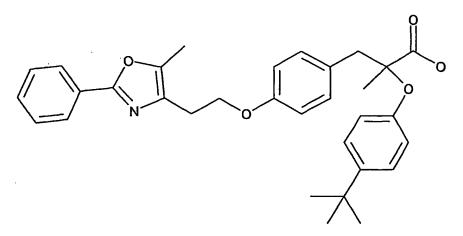
(EI) 534.2 (M + H)⁺ shown below, were synthesized according to the procedure of Example 13, Steps D and E, respectively from toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-5-methyl-oxazol-4-yl)-ethyl ester, and then purified by LC/MS:

MS (EI) 506.1 (M + H)⁺; LC RT = 3.12 min (>99% pure).

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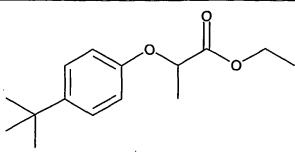
Example 16

3-{4-[2-(2-Pheny1-5-methyl-oxazo1-4-y1)-ethoxy]-pheny1}-2-methyl-2-(4-tert-butylphenoxy)-propionic acid



Step A

2-(4-tert-Butyl-phenoxy)-propionic acid ethyl ester



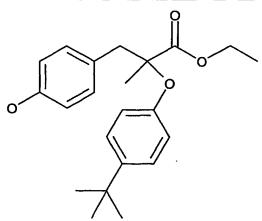
10

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4-t-Butylphenol (7.52 g, 50 mmol) in anhydrous DMF (40 mL) was added dropwise to NaH (2.2 g, 55 mmol, 60% w/w in mineral oil) at 0 °C under an atmosphere of nitrogen. After five min, ethyl 2-bromopropionate (6.49 mL, 50 mmol, d=1.394) was added rapidly dropwise and the resultant mixture was allowed to stir for 18 h, gradually warming to ambient temperature. The reaction mixture was diluted with ethyl acetate (300 mL) and extracted twice with water and once with brine. The organic layer was dried over Na2SO4 and 10 concentrated in vacuo to produce a colorless oil (12.5 g, 100%) ¹H NMR (300 MHz, CDCl₃): δ 7.28 (d, 2H, J=5.5), 6.80 (d, 2H, J=5.5), 4.70 (q, 1H, J=6.6), 4.22 (q, 2H, J=7.1),1.59 (d, 3H, J=6.6), 1.28 (s, 9H), 1.25 (t, 3H, J=7.1). MS [EI+] 251 $(M+H)^+$, 268 $(M+NH_4)^+$. 15

Step B
2-(4-tert-Butyl-phenoxy)-3-(4-hydroxyphenyl)-2methylpropionic acid ethyl ester



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A solution of LDA (12.7 mL, 19.1 mmol, 1.5M in cyclohexane) was cooled to -78 °C in a dry ice/acetone bath and then added to a solution of 2-(4-tert-butyl-phenoxy)-

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propionic acid ethyl ester in anhydrous THF (20 mL) also cooled to -78 °C under an atmosphere of nitrogen. After five min, 4-benzyloxybenzaldehyde (3.69 g, 17.4 mmol) was added in one portion. After stirring for 10 min, the reaction mixture was quenched with saturated solution of aqueous NH₄Cl (10 mL) and the mixture allowed to warm to ambient temperature. The biphasic mixture was diluted with ether (100 mL) and partitioned, and the organic layer was washed with brine, dried over MgSO4 and concentrated in vacuo. The residue was purified by flash column chromatography (600 g silica, 25x200mL fractions, gradient elution 0-20% ethyl acetate in hexanes) to provide a colorless oil (3.46 g, 58%) as a mixture of inseparable diastereomers of 3-(4-benzyloxyphenyl)-2-(4-tert-butyl-phenoxy)-3-hydroxy-2-methylpropionic acid ethyl ester which was used without further characterization or purification.

3-(4-Benzyloxy-phenyl)-2-(4-tert-butyl-phenoxy)-3-hydroxy-2-methylpropionic acid ethyl ester (3.46 g, 7.5 mmol) in anhydrous CH₂Cl₂ (50 mL) was cooled to 0 °C and treated with pyridine (6.0 mL, 75 mmol, d=0.978).

Trifluoroacetic anhydride (2.11 mL, 15 mmol, d=1.487) was added dropwise and the mixture was stirred for 1 h,

was used without characterization.

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gradually warming to ambient temperature. The solution was washed twice with 1N HCl and the organic layer dried over Na₂SO₄ and concentrated in vacuo to produce 3-(4-benzyloxyphenyl)-2-(4-tert-butyl-phenoxy)-3-trifluoroacetoxy-2-methylpropionic acid ethyl ester which

The material was dissolved in ethyl acetate (50 mL) and treated with 10% palladium on carbon (1.5 g), and stirred under an atmosphere of hydrogen for 48 h. The suspension was filtered through celite and concentrated in vacuo to a golden oil. The residue was purified by flash column chromatography (200 g silica, 30x20mL fractions, 2% ethyl acetate in CHCl₃) to provide the title compound as a colorless oil (1.06 g, two steps 40%) ¹H NMR (300 MHz, CDCl₃): δ 7.21 (d, 2H, J=8.6), 7.12 (d, 2H, J=8.6), 4.19 (q, 1H, J=7.1), 3.24 (d, 1H, J=12.3), 3.11 (d, 1H, J=12.3), 1.38 (s, 3H), 1.27 (s, 9H), 1.23 (t, J=7.1). MS [EI+] 357 (M+H)⁺, [EI-] 355 (M-H)⁺.

Step C

3-{4-[2-(2-Pheny1-5-methy1-oxazo1-4-y1)-ethoxy]-pheny1}-2methy1-2-(4-tert-buty1phenoxy)-propionic acid

The title compound was prepared using the representative Standard Procedure (A) from 3-(4-

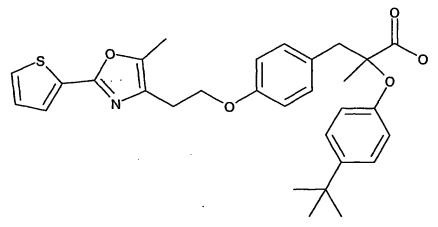
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hydroxyphenyl)-2-methyl-2-(4-tert-butylphenoxy)-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-phenyl)-oxazol-4-yl)-ethyl ester to produce a white solid (17%). MS [EI+] 514 (M+H)⁺, [EI-] 512 (M-H)⁺.

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Example 17

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-tert-butylphenoxy)-propionic acid



The title compound was prepared, according to the procedure of Example 16, Step C, using 3-(4-hydroxyphenyl)-2-methyl-2-(4-tert-butylphenoxy)-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester to produce a white solid (19%). MS

[EI+] 520 (M+H)+, [EI-] 518 (M-H)+.

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Example 18

2-Methyl-3-(4-{2-[5-methyl-2-cyclohexylyl-oxazol-4-yl]-ethoxy}-phenyl)-2-(4-tert-butylphenoxy)-propionic acid

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The title compound was prepared, according to the procedure of Example 16, Step C, using 3-(4-hydroxyphenyl)-2-methyl-2-(4-tert-butylphenoxy)-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-cyclohexylyl-oxazol-4-yl)-ethyl ester to produce a white solid (18%). MS
[EI+] 520 (M+H)⁺, [EI-] 518 (M-H)⁺

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Example 19

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-methoxyphenoxy)-propionic acid

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Step A

2-(4-Methoxyphenoxy)-propionic acid ethyl ester

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4-Methoxyphenol (3.29 g, 26.5 mmol), K_2CO_3 (7.32 g, 53 mmol), and ethyl 2-bromopropionate (4.8 g, 26.5 mmol) were combined in anhydrous DMF (50 mL) and stirred at 90 °C under an atmosphere of nitrogen. After 16 h, the DMF was removed in vacuo. The residue was dissolved in ethyl acetate (100 mL) and washed twice with water and once with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to produce a golden oil (4.8 g, 81%) ¹H NMR (250 MHz, CDCl₃): δ 6.76 (d, 2H, J=7.9), 6.73 (d, 2H, J=7.9), 4.58 (q, 1H, J=6.1), 4.14 (q, 2H, J=7.2), 3.69 (s, 3H), 1.52 (d, 3H,

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J=6.1), 1.19 (t, 3H, J=7.2). MS [EI+] 225 (M+H)⁺, [EI-] 223 (M-H)⁺.

Step B

5 <u>2-(4-Methoxyphenoxy)-3-(4-benzyloxyphenyl)-2-methylpropionic</u> acid ethyl ester

A solution of 2-(4-methoxyphenoxy)-propionic acid ethyl ester in anhydrous THF (20 mL) was cooled to -78 °C under 10 nitrogen and then treated with dropwise addition of LDA (13.4 mL, 20 mmol, 1.5M in cyclohexane) at a rate slow enough to keep the temperature below -70 °C. After 30 min, 4-benzyloxybenzaldehyde (3.88 g, 18.3 mmol) in anhydrous THF was added slowly dropwise in the fashion previously 15 described. After stirring for 30 min, the reaction mixture was quenched with saturated solution of aqueous NH4Cl (20 mL) and the mixture was warmed to ambient temperature. The biphasic mixture was diluted with ether (100 mL) and partitioned, and the organic layer was washed with brine, 20 dried over MgSO4 and concentrated in vacuo. The residue was purified by flash column chromatography (500 g silica, 40x125mL fractions, gradient elution 0-20% ethyl acetate in hexanes) to provide a colorless oil (3.97 g, 50%) as a

mixture of inseparable diastereomers of 3-(4-benzyloxy-phenyl)-2-(4-methoxyphenoxy)-3-hydroxy-2-methylpropionic acid ethyl esterwhich was used without further characterization or purification. R_f =0.28 in 4:1 hexanes:ethyl acetate.

3-(4-Benzyloxyphenyl)-2-(4-methoxyphenoxy)-3-hydroxy-2methylpropionic acid ethyl ester (2.15 g, 4.9 mmol) in anhydrous CH2Cl2 (30 mL) was cooled to 0 °C and treated with BF_3-Et_2O (0.91 mL, 7.4 mmol, d=1.154) and triethylsilane 10 (1.18 mL, 7.4 mmol, d=0.728). The mixture was stirred for 2 h, gradually warming to ambient temperature. Saturated aqueous Na₂CO₃ (15 mL) was added and the mixture was stirred vigorously. The solution was partitioned and the organic layer was washed twice with water and brine, dried over Na₂SO₄, and concentrated in vacuo to produce 3-(4-benzyloxy-15 phenyl)-2-(4-methoxyphenoxy)-2-methylpropionic acid ethyl ester as a colorless oil (428 mg, 21%). $R_f=0.36$ in 4:1 hexanes:ethyl acetate ^{1}H NMR (300 MHz, CDCl₃): δ 7.45 (t, 2H, J=7.1), 7.35 (d, 2H, J=7.1), 7.34 (t, 1H, J=7.0), 7.18 (d, 2H, 8.6), 6.91 (d, 2H, J=6.6), 6.79 (d, 2H, 8.6), 6.74 (d, 20 2H, J=6.6), 5.05 (s, 2H), 4.21 (q, 1H, J=7.1), 3.75 (s, 3H), 3.23 (d, 1H, J=13.7), 3.10 (d, 1H, J=13.7), 1.31 (s, 3H), 1.25 (t, 3H, J=7.1). MS [EI+] 438 (M+NH₄)⁺, [EI-] 419 (M-H)⁺.

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Step C

2-(4-Methoxyphenoxy)-3-(4-hydroxyphenyl)-2-methylpropionic acid ethyl ester

3-(4-Benzyloxy-phenyl)-2-(4-methoxyphenoxy)-2-5 methylpropionic acid ethyl ester (428 mg, 1.0 mmol) was dissolved in ethanol (50 mL) and treated with 5% palladium on carbon (200 mg), and stirred under an atmosphere of hydrogen for 16 h. The suspension was filtered through 10 celite and concentrated in vacuo to provide a colorless oil. (257 mg, 76%) ¹H NMR (300 MHz, CDCl₃): δ 7.06 (d, 2H, J=8.6), 6.73 (d, 2H, J=6.6), 6.72 (d, 2H, J=8.6), 6.69 (t, 1H, J=6.6), 4.16 (q, 1H, J=7.4), 3.68 (s, 3H), 3.14 (d, 1H, J=13.7), 3.01 (d, 1H, J=13.7), 1.23 (s, 3H), 1.18 (t, J=7.4). MS [EI+] 331 (M+H)⁺, 348 (M+NH₄)⁺, [EI-] 329 (M-H)⁺. 15 2-(4-Methoxyphenoxy)-3-(4-hydroxyphenyl)-2methylpropionic acid ethyl ester (515821) (approx. 2.5 g) prepared in the same manner was purified by chiral chromatography to provide the individual enantiomers 20 (Chiracel OD, 8 x 29 cm, 5% IPA/heptane, 275 nm; (S)-isomer: 1.09 g, 97.4% ee, (R)-isomer: 1.01 g, >99% ee).

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Step D

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-methoxyphenoxy)-propionic acid ethyl

ester

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Prepared from 3-(4-hydroxypheny1)-2-methy1-2-(4-methoxyphenoxy)-propionic acid ethyl ester and toluene-4
10 sulfonic acid 2-(5-methy1-2-thiophen-2-y1-oxazo1-4-y1)-ethyl ester to produce a colorless oil (86%). ¹H NMR (300 MHz, CDC1₃): 8 7.57 (d, 1H, J=3.5), 7.36 (d, 1H, J=5.1), 7.15 (d, 2H, J=8.6), 7.07 (dd, 1H, J=5.1,3.5), 6.81 (d, 2H, J=6.6), 6.78 (d, 2H, J=8.6), 6.71 (d, 2H, J=6.6), 4.21 (q, 2H, J=7.2), 4.20 (t, 2H, J=6.4), 3.74 (s, 3H), 3.21 (d, 1H, J=13.7), 3.08 (d, 1H, J=13.7), 2.95 (t, 2H, J=6.4), 2.35 (s, 3H), 1.28 (s, 3H), 1.25 (t, 3H, J=7.2). MS [EI+] 522 (M+H)⁺.

Step E

20 <u>2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-</u> ethoxy]-phenyl}-2-(4-methoxyphenoxy)-propionic acid

The title compound was prepared from 2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-methoxyphenoxy)-propionic acid ethyl ester using the

hydrolysis procedure of Example 1, Step E, to provide a white solid (63%). 1 H NMR (300 MHz, d₆-DMSO): δ 7.70 (d, 1H, J=4.8), 7.57 (d, 1H, J=3.9), 7.15 (dd, 1H, J=4.8,3.9), 7.10 (d, 2H, J=8.6), 6.83 (d, 2H, J=8.6), 6.76 (d, 2H, J=9.0), 6.71 (d, 2H, J=9.0), 4.12 (t, 2H, J=6.4), 3.65 (s, 3H), 3.07 (d, 1H, J=13.7), 3.06 (d, 1H, J=13.7), 2.86 (t, 2H, J=6.4), 2.30 (s, 3H), 1.20 (s, 3H). MS [EI+] 494 (M+H)⁺, [EI-] 492 (M-H).

Example 20

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(S) -2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-methoxyphenoxy)-propionic acid

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Step A

(S) -2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-methoxyphenoxy)-propionic acid ethyl

ester

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The title compound was prepared from (S)-3-(4-hydroxypheny1)-2-methy1-2-(4-methoxyphenoxy)-propionic acid ethy1 ester and toluene-4-sulfonic acid 2-(5-methy1-2-thiophen-2-yl-oxazol-4-yl)-ethy1 ester to produce a colorless oil (32%). ¹H NMR (300 MHz, CDCl₃): δ 7.57 (d, 1H, J=3.5), 7.36 (d, 1H, J=5.1), 7.15 (d, 2H, J=8.6), 7.07 (dd, 1H, J=5.1,3.5), 6.81 (d, 2H, J=6.6), 6.78 (d, 2H, J=8.6), 6.71 (d, 2H, J=6.6), 4.21 (q, 2H, J=7.2), 4.20 (t, 2H, J=6.4), 3.74 (s, 3H), 3.21 (d, 1H, J=13.7), 3.08 (d, 1H, J=13.7), 2.95 (t, 2H, J=6.4), 2.35 (s, 3H), 1.28 (s, 3H), 1.25 (t, 3H, J=7.2). MS [EI+] 522 (M+H)⁺.

20 Step B

(S)-2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-methoxyphenoxy)-propionic acid

The title compound was prepared from (S)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2
(4-methoxyphenoxy)-propionic acid ethyl ester, according to the procedure of Example 19, Step E, to provide a sticky

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white solid (83%). ¹H NMR (300 MHz, d₆-DMSO): δ 7.70 (d, 1H, J=4.8), 7.57 (d, 1H, J=3.9), 7.15 (dd, 1H, J=4.8,3.9), 7.10 (d, 2H, J=8.6), 6.83 (d, 2H, J=8.6), 6.76 (d, 2H, J=9.0), 6.71 (d, 2H, J=9.0), 4.12 (t, 2H, J=6.4), 3.65 (s, 3H), 3.07 (d, 1H, J=13.7), 3.06 (d, 1H, J=13.7), 2.86 (t, 2H, J=6.4), 2.30 (s, 3H), 1.20 (s, 3H). MS [EI+] 494 (M+H)⁺, [EI-] 492 (M-H).

Example 21

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2-(3-Fluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

 $2-(3-\text{Fluoro-phenoxy})-2-\text{methyl}-3-\{4-[2-(5-\text{methyl}-2-\text{phenyl}-\text{oxazol}-4-\text{yl})-\text{ethoxy}]-\text{phenyl}\}-\text{propionic acid was}$ obtained from 2-(3-fluoro-phenoxy)-3-(4-hydroxyphenyl)-2-methyl-propionic acid ethyl ester by the Standard Procedure (B). ^1H NMR (400 MHz, CDCl₃) δ 7.99-7.97 (m, 2H), 7.47-7.45 (m, 3H), 7.21-7.15 (m, 3H), 6.82 (d, 2H, J = 8.2 Hz), 6.76-6.61 (m, 3H), 4.20 (t, 2H, J = 6.3 Hz), 3.26 (d, 1H, J = 14.1 Hz), 3.12 (d, 1H, J = 14.1 Hz), 3.05 (t, 2H, J = 6.3 Hz), 2.42 (s, 3H), 1.44 (s, 3H). HRMS (ES⁺) m/z exact mass calcd for $C_{28}H_{26}FNO_5$ 476.1873, found 476.1869.

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Example 22

2-(3-Fluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound wasprepared from 2-(3-fluorophenoxy)-3-(4-hydroxyphenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester according to the method of Example 21. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, 1H, J = 3.5 Hz, 1.17 Hz), 7.41 (dd, 1H, J = 5.1 Hz, 1.17 Hz), 7.19-7.16 (m, 3H), 7.08 (dd, 1H, J = 5.1 Hz, 3.91 Hz), 6.81 (d, 2H, J = 8.6 Hz), 6.75-6.62 (m, 3H), 4.17 (t, 2H, J = 6.6 Hz), 3.26 (d, 1H, J = 13.7 Hz), 3.14 (d, 1H, J = 13.69 Hz), 2.98 (t, 2H, J = 6.65 Hz), 2.36 (s, 3H), 1.45 (s, 3H). HRMS (ES⁺) m/z exact mass calcd for C₂₆H₂₅FNO₅S 482.1437, found 482.1454.

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Example 23

2-(3-Fluoro-phenoxy)-2-methy1-3-{4-[2-(5-methy1-2-cyclohexy1-oxazo1-4-y1)-ethoxy]-pheny1}-propionic acid

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The title compound wasprepared from 2-(3-fluoro-phenoxy)-3-(4-hydroxypheny1)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester according to the method of Example

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¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, 1H, J = 7.8 Hz), 7.57 (d, 2H, J = 7.8 Hz), 7.50-7.27 (m, 5H), 7.12 (m, 3H), 6.76 (d, 2H, J = 8.6 Hz), 6.72-6.58 (m, 3H), 4.14 (t, 2H, J = 6.7 Hz), 3.18 (d, 1H, J = 14.1 Hz), 3.08 (d, 1H, J = 14.1 Hz), 2.94 (t, 2H, J = 6.7 Hz), 2.37 (s, 3H), 1.38 (s, 3H). MS (ES⁺) m/z mass calcd for $C_{34}H_{31}FNO_{5}$ 552.21, found 552.2.

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Example 24

2-(3-tert-Butyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

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2-(3-t-Butyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid was obtained from 2-(3-tert-butyl-phenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester by the Standard

10 Procedure (B). ¹H NMR (400 MHz, CDCl₃) δ 7.19-7.16 (m, 3H), 7.08 (dt, 1H, J = 7.0 Hz, 0.8 Hz), 7.92 (t, 1H, J = 2.0 Hz), 6.83 (d, 2H, J = 8.6 Hz), 6.72-6.99 (m, 1H), 4.21 (t, 2H, J = 6.3 Hz), 3.25 (d, 1H, J = 14.1 Hz), 3.15 (d, 1H, J = 14.1 Hz), 3.00 (t, 2H, J = 6.3 Hz), 2.39 (s, 3H), 1.43 (s, 3H), 1.25 (s, 9H). HRMS (ES⁺) m/z exact mass calcd for C₃₂H₃₅₄NO₅ 514.2593, found 514.2622.

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Example 25

2-(3-tert-Butyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

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Example 26

2-(2-Fluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

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 $2-(2-\text{Fluorophenoxy})-2-\text{methyl}-3-\{4-[2-(5-\text{methyl}-2-\text{phenyl}-\text{oxazol}-4-\text{yl})-\text{ethoxy}]-\text{phenyl}\}-\text{propionic acid was} \\ \text{prepared from } 2-(2-\text{fluorophenoxy})-3-(4-\text{hydroxy-phenyl})-2-\\ \text{methyl-propionic acid ethyl ester by the parallel synthesis} \\ \text{method (B).} \ ^1\text{H NMR (400 MHz, CDCl}_3) \ \delta \ 7.96 \ (dd, 2\text{H, J} = 7.43 \text{Hz}, 2.35 \text{ Hz}), 7.42-7.40 \ (m, 3\text{H}), 7.22 \ (d, 2\text{H, J} = 8.99 \text{ Hz}), \\ 7.12-6.95 \ (m, 4\text{H}), 6.84 \ (d, 2\text{H, J} = 8.60 \text{ Hz}), 4.20 \ (t, 2\text{H, J} = 6.65 \text{ Hz}), 3.26 \ (d, 1\text{H, J} = 14.08 \text{ Hz}), 3.18 \ (d, 1\text{H, J} = 14.08 \text{ Hz}), 2.99 \ (t, 2\text{H, J} = 6.65 \text{ Hz}), 2.38 \ (s, 3\text{H}), 1.42 \ (s, 3\text{H}). \\ \text{HRMS (ES}^+) \ \text{m/z exact mass calcd for C}_{28\text{H}_{26}\text{FNO}_{5}} \ 476.1873, \\ \text{found 476.1858}. \\ \end{aligned}$

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Example 27

2-(2-Fluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared from 2-(2-fluorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester by the procedure of Example 26. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, 1H, J = 3.52 Hz, 1.17 Hz), 7.36 (dd, 1H, J = 5.08 Hz, 1.17 Hz), 7.21 (d, 3H, J = 8.60 Hz), 7.12-6.95 (m, 3H), 6.83 (d, 3H, J = 8.60 Hz), 4.19 (t, 2H, J = 6.65 Hz), 3.27 (d, 1H, J = 14.08 Hz), 3.17 (d, 1H, J = 14.08 Hz), 2.95 (t, 2H, J = 6.65 Hz), 2.35 (s, 3H), 1.41 (s, 3H). HRMS (ES⁺) m/z exact mass calcd for C₂₆H₂₅FNO₅S 482.1437, found 482.1454.

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Example 28

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-fluoro-phenoxy)-2-methyl-propionic acid

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The title compound was prepared from 2-(2-fluorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester by the procedure of Example 26. ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, 2H, J = 8.60 Hz), 7.12-6.96 (m, 4H), 6.79 (d, 2H, J = 8.60 Hz), 4.15 (t, 2H, J = 6.65 Hz), 3.26 (d, 1H, J = 14.08 Hz), 3.19 (d, 1H, J = 14.08 Hz), 2.98-2.80 (m, 2H), 2.32 (s, 3H), 2.02 (d, 2H, J = 10.95 Hz), 1.81 (d, 2H, J = 12.90 Hz), 1.70 (d, 1H, J = 12.90 Hz), 1.85 (q, 2H, J = 11.73 Hz), 1.40 (s, 3H), 1.39-1.23 (m, 3H). HRMS (ES⁺) m/z exact mass calcd for C₂₈H₃₃FNO₅ 482.2343, found 482.2349.

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Example 29

2-(4-Chloro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

5 2-(4-Chlorophenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid was obtained from 2-(4-chlorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester by the Standard Procedure (B). ¹H NMR (400 MHz, CDCl₃) δ 7.98-7.96 (m, 2H), 7.45 (d, 3H, J = 6.65 Hz), 7.17 (t, 4H, J = 7.43 Hz), 6.82 (dd, 4H, J = 8.60 Hz, 2.74 Hz), 4.20 (t, 2H, J = 6.26 Hz), 3.23 (d, 1H, J = 14.08 Hz), 3.12 (d, 1H, J = 14.08 Hz), 3.04 (t, 2H, J = 6.26 Hz), 2.41 (s, 3H), 1.39 (s, 3H). MS (ES⁺) m/z mass calcd for C₂₈H₂₇ClNO₅ 492.16, found 492.2.

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Example 30

2-(4-Chlorophenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared from 2-(4-chlorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester by the procedure of Example 29. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, 1H, J = 4.30 Hz), 7.38 (d, 1H, J = 4.30 Hz), 7.20-7.16 (m, 4H), 7.06 (dd, 1H, J = 8.60 Hz, 3.91 Hz), 6.83 (t, 4H, J = 8.60 Hz), 4.17 (t, 2H, J = 6.65 Hz), 3.23 (d, 1H, J = 14.08 Hz), 3.14 (d, 1H, J = 14.08 Hz), 2.97 (t, 2H, J = 6.65 Hz), 2.36 (s, 3H), 1.41 (s, 3H). MS (ES⁺) m/z mass calcd for C₂₆H₂₅ClNO₅S 498.12, found 498.1.

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Example 31

2-(4-Chlorophenoxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid

The title compound was prepared from 2-(4-chlorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester by the procedure of Example 29. ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, 2H, J = 8.60 Hz), 7.16 (d, 2H, J = 8.60 Hz), 6.83 (d, 2H, J = 8.60 Hz), 6.79 (d, 2H, J = 8.60 Hz), 4.12 (t, 2H, J = 6.26 Hz), 3.21 (d, 1H, J = 14.08 Hz), 3.11 (d, 1H, J = 14.08 Hz), 2.95 (t, 2H, J = 6.26 Hz), 2.89-2.83 (m, 3H), 2.05 (d, 2H, J = 11.73 Hz), 1.80 (d, 2H, J = 11.73 Hz), 1.55 (q, 2H, J = 11.73 Hz), 1.40 (s, 3H), 1.37-1.20 (m, 4H). MS (ES⁺) m/z mass calcd for C₂₈H₃₃ClNO₅ 498.21, found 498.2.

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Example 32

 $2-(4-Cyclohexyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2$ phenyl-oxazol-4-yl)-ethoxyl-phenyl}-propionic acid

 $2-(4-Cyclohexyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-$ 5 phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid was obtained from 2-(4-cyclohexylphenoxy)-3-(4-hydroxyphenyl)-2methylpropionic acid ethyl ester by the Standard Procedure (B). 1 H NMR (400 MHz, CDCl₃) δ 7.99-7.98 (m, 2H), 7.45 (t, 3H, J = 2.80 Hz), 7.18 (d, 2H, J = 8.60 Hz), 7.08 (d, 2H, J10 = 7.90 Hz), 6.82 (d, 4H, J = 8.60 Hz), 4.21 (t, 2H, J = 6.26 Hz), 3.22 (d, 1H, J = 14.08 Hz), 3.12 (d, 1H, J = 14.08 Hz), 2.40 (s, 4H), 1.83-1.71 (m, 5H), 1.40 (s, 3H), 1.38-1.16 (m, 6H). MS (ES †) m/z mass calcd for C₃₄H₃₈NO₅ 540.28, found 15 540.3.

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Example 33

2-(4-Cyclohexyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared from 2-(4cyclohexylphenoxy)-3-(4-hydroxypheny1)-2-methylpropionic
acid ethyl ester by the method of Example 32. ¹H NMR (400
MHz, CDCl₃) δ 7.68 (d, 1H, J = 3.13 Hz), 7.43 (dd, 1H, J =
4.69 Hz, 0.78 Hz), 7.18 (d, 2H, J = 8.60 Hz), 7.10 (dd, 1H,

J = 5.08 Hz, 3.52 Hz), 7.08 (d, 2H, J = 8.60 Hz), 6.87-6.80
(m, 4H), 4.19 (t, 2H, J = 6.26 Hz), 3.39 (s, 5H), 3.23 (d,
1H, J = 14.08 Hz), 3.11 (d, 1H, J = 14.08 Hz), 2.99 (t, 2H,
J = 6.26 Hz), 2.37 (s, 3H), 1.82 (d, 4H, J = 11.73 Hz), 1.73
(d, 1H, J = 11.73 Hz), 1.40 (s, 3H). MS (ES⁺) m/z mass

calcd for C₃₂H₃₆NO₅S 546.23, found 546.2.

Example 34

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-(4-cyclohexyl-phenoxy)-2-methyl-propionic acid

The title compound was prepared from 2-(4cyclohexylphenoxy)-3-(4-hydroxyphenyl)-2-methylpropionic
acid ethyl ester by the method of Example 32. ¹H NMR (400
MHz, CDCl₃) δ 7.18 (d, 2H, J = 8.60 Hz), 7.08 (d, 2H, J =
8.60 Hz), 6.80 (q, 4H, J = 8.60 Hz), 4.14 (t, 2H, J = 6.26
10 Hz), 3.38 (s, 6H), 3.22 (d, 1H, J = 14.08 Hz), 3.12 (d, 1H,
J = 14.08 Hz), 2.96 (t, 2H, J = 6.26 Hz), 2.92-2.83 (m, 2H),
2.30 (s, 3H), 2.02 (d, 2H, J = 10.56), 1.81-1.78 (m, 6H),
1.76-1.68 (m, 2H), 1.59-1.50 (m, 2H), 1.40 (s, 3H). MS
(ES⁺) m/z mass calcd for C₃₄H₄₄NO₅ 546.32, found 546.3.

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Example 35

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-(3,4-dimethyl-phenoxy)-2-methyl-propionic acid

The representative parallel synthesis procedure (B) was 5 used to prepare the title compound from 2-(3,4dimethylphenoxy)-3-(4-hydroxyphenyl)-2-methylpropionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5methyl-oxazol-4-yl)-ethyl ester. 1 H NMR (400 MHz, CDCl₃) δ 7.18 (d, 2H, J = 8.4 Hz), 6.99 (d, 1H, J = 8.4 Hz), 6.79 (d,10 2H, J = 8.4 Hz), 6.71 (d, 1H, J = 2.4 Hz), 6.64 (dd, 1H, J =8.4, 2.4 Hz), 4.16 (t, 2H, J = 6.0 Hz), 3.21 and 3.11 (d of Abq, 2H, J = 14.0 Hz), 2.98 (t, 2H, J = 6.0 Hz), 2.91 (tt, 1H, J = 11.4, 3.2 Hz), 2.31 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 2.06-2.02 (m, 2H), 1.85-1.79 (m, 2H), 1.73-1.68 (m, 15 1H), 1.62-1.51 (m, 2H), 1.42-1.22 (m, 3H), 1.39 (s, 3H). IR (KBr) 3500, 2935, 1735, 1612, 1513, 1249, 1178 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for $C_{30}H_{38}NO_5$ 492.2750, found 492.2751.

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Example 36

2-(3,4-Dimethyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

5 The procedure of Example 35 was used to prepare the title compound from 2-(3,4-dimethylphenoxy)-3-(4hydroxyphenyl)-2-methylpropionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thipohen-2-yl-oxazol-4-yl)-ethyl ester. 1 H NMR (400 MHz, CDCl₃) δ 7.73 (d, 1H, J = 3.2 Hz), 7.46 (d, 1H, J = 4.8 Hz), 7.18 (d, 2H, J = 8.410 Hz), 7.13-7.10 (m, 1H), 7.06 (bs, 1H), 6.99 (d, 1H, J = 8.0Hz), 6.81 (d, 2H, J = 8.4 Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.63 (dd, 1H, J = 8.0, 2.4 Hz), 4.20 (t, 2H, J = 6.0 Hz), 3.23 and 3.11 (d of Abq, 2H, J = 14.0 Hz), 3.02 (t, 2H, J =6.0 Hz), 2.38 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.39 (s,15 3H). IR (KBr) 3500, 3000, 1729, 1512, 1250, 1178 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for C₂₈H₃₀NO₅S 492.1845, found 492.1845.

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Example 37

2-(3,4-Dimethyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The representative parallel synthesis procedure (B) was used to prepare the title compound from 2-(3,4-dimethyl-phenoxy)-3-(4-hydroxyphenyl)-2-methylpropionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 8.01-7.99 (m, 2H), 7.48-7.46 (m, 3H), 7.18 (d, 2H, J = 8.8 Hz), 6.99 (d, 1H, J = 8.4 Hz), 6.82 (d, 2H, J = 8.4 Hz), 6.70 (d, 1H, J = 2.0 Hz), 6.63 (dd, 1H, J = 8.4, 2.0 Hz), 6.28 (bs, 1H), 4.22 (t, 2H, J = 6.4 Hz), 3.22 and 3.11 (d of Abq, 2H, J = 13.6 Hz), 3.06 (t, 2H, J = 6.4 Hz), 2.42 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.39 (s, 3H). IR (KBr) 3100, 2950, 1772, 1611, 1512, 1177 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for C₃₀H₃₂NO₅ 486.2280, found 486.2295.

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Example 38

2-(3,4-Dimethyl-phenoxy)-2-methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid

5

The representative parallel synthesis procedure (B) was used to prepare the title compound from 2-(3,4-dimethylphenoxy)-3-(4-hydroxyphenyl)-2-methylpropionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-(1-10 methylcyclohexyl)-oxazol-4-yl)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 7.10 (d, 2H, J = 8.60 Hz), 6.92 (d, 1H, J = 8.60 Hz), 6.73 (d, 2H, J = 8.99 Hz), 6.64 (d, 1H, J = 2.35 Hz), 6.57 (dd, 1H, J = 8.21 Hz, J = 3.13 Hz), 4.06 (t, 2H, J = 6.25 Hz), 3.14 (d, 1H, J = 14.08 Hz), 3.04 (d, 1H, J = 14.08 Hz), 2.85 (t, 2H, J = 6.25 Hz), 2.19 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.07-2.01 (m, 2H), 1.53-1.28 (m, 8H), 1.36 (s, 3H), 1.20 (s, 3H); MS (ES[†]) calcd for C₃₁H₄₀NO₅: Found m/e 506.3 (M + 1, 100%).

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Example 39

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-p-tolyloxy-propionic acid

The representative procedure (B) was utilized to prepare the title compound from 3-(4-hydroxyphenyl)-2-methyl-2-p-tolyloxypropionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester.

¹H NMR (400 MHz, CDCl₃) δ 8.05 (bs, 1H), 8.02-7.96 (m, 2H),

7.51-7.45 (m, 3H), 7.18 (d, 2H, J = 8.4 Hz), 7.05 (d, 2H, J = 8.4 Hz), 6.81 and 6.81 (d of Abq, 4H, J = 8.0 Hz), 4.22 (t, 2H, J = 6.0 Hz), 3.23 and 3.11 (d of Abq, 2H, J = 14.0 Hz), 3.06 (t, 2H, J = 6.0 Hz), 2.42 (s, 3H), 2.28 (s, 3H), 1.38 (s, 3H). IR (KBr) 3420, 1718, 1712, 1508, 1228 cm⁻¹.
HRMS (ES⁺) m/z exact mass calcd for C₂9H₃0NO5 472.2124, found 474.2139.

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Example 40

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-p-tolyloxy-propionic acid

The representative procedure (B) was utilized to prepare the title compound from 3-(4-hydroxyphenyl)-2-methyl-2-p-tolyloxypropionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester.

1H NMR (400 MHz, CDCl₃) δ 10.0 (bs, 1H), 7.59 (dd, 1H, J = 3.8, 1.2 Hz), 7.36 (dd, 1H, J = 5.0, 1.2 Hz), 7.19 (d, 2H, J = 8.4 Hz), 7.05 (dd, 1H, J = 5.0, 3.8 Hz), 7.02 (d, 2H, J = 8.0 Hz), 6.83-6.80 (m, 4H), 4.17 (t, 2H, J = 6.4 Hz), 3.29 and 3.14 (d of Abq, 2H, J = 13.8 Hz), 2.96 (t, 2H, J = 6.4 Hz), 2.35 (s, 3H), 2.27 (s, 3H), 1.38 (s, 3H). IR (KBr) 3420, 1715, 1509, 1225 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for C₂₇H₂₈NO₅S 478.1688, found 478.1714.

Example 41

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-p-tolyloxy-propionic acid

The representative procedure (B) was utilized to prepare the title compound from 3-(4-hydroxyphenyl)-2-methyl-2-p-tolyloxypropionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 10.90 (bs, 1H), 7.18 (d, 2H, J = 8.4 Hz), 7.05 (d, 2H, J = 8.4 Hz), 6.79 and 6.79 (d of Abq, 4H, J = 8.0 Hz), 4.15 (t, 2H, J = 6.0 Hz), 3.23 and 3.11 (d of Abq, 2H, J = 13.8 Hz), 3.02-2.93 (m, 3H), 2.34 (s, 3H), 2.29 (s, 3H), 2.10-2.00 (m, 2H), 1.89-1.80 (m, 2H), 1.77-1.70 (m, 1H), 1.64-1.51 (m, 2H), 1.45-1.19 (m, 3H), 1.38 (s, 3H). IR (KBr) 3450, 1734, 1509, 1228 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for C₂₉H₃₆NO₅ 478.2593, found 478.2613.

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The following compounds were prepared from (S)-3-(4-hydroxyphenyl)-2-methyl-2-p-tolyloxypropionic acid ethyl ester (96% ee, Chiracel OD separation, 8 x 29 cm, 7% IPA/heptane, 275 nm) by the procedure described in Example 1: (S)-2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-p-tolyloxy-propionic acid and(S)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-p-tolyloxy-propionic acid.

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Example 42

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-trifluoromethoxy-phenoxy)-propionic acid

5

The representative procedure (B) was utilized to prepare the title compound from 3-(4-hydroxy-phenyl)-2-methyl-2-(4-trifluoromethoxy-phenoxy)-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-0xazol-4-yl)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 7.79-7.94 (m, 2H), 7.43-7.41 (m, 3H), 7.18 (d, 2H, J = 8.8 Hz), 7.07 (d, 2H, J = 8.4 Hz), 6.89 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.4 Hz), 4.19 (t, 2H, J = 6.4 Hz), 3.24 and 3.14 (d of Abq, 2H, J = 14.0 Hz), 3.01 (t, 2H, J = 6.4 Hz), 3.00 (bs, 1H), 2.39 (s, 3H), 1.42 (s, 3H). IR (KBr) 3600, 2980, 1725, 1611, 1504, 1265 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for C₂₉H₂₇NO₆ F₃ 542.1790, found 542.1802.

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Example 43

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-trifluoromethoxy-phenoxy)-propionic acid

5

The title compound was prepared from 3-(4-hydroxy-phenyl)-2-methyl-2-(4-trifluoromethoxy-phenoxy)-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester using the procedure of Example 42. ¹H NMR (400 MHz, CDCl₃) & 7.70-7.67 (m, 1H), 7.41 (dd, 1H, J = 5.2, 1.2 Hz), 7.17 (d, 2H, J = 8.8 Hz), 7.11-7.07 (m, 3H), 6.90 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.8 Hz), 4.20 (t, 2H, J = 6.6 Hz), 3.25 and 3.14 (d of Abq, 2H, J = 14.0 Hz), 2.99 (t, 2H, J = 6.4 Hz), 2.37 (s, 3H), 1.43 (s, 3H). IR (KBr) 3600, 3000, 1727, 1611, 1504, 1265 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for C₂₇H₂₅NO₆F₃S 548.1354, found 548.1362.

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Example 44

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-(4-trifluoromethoxy-phenoxy)-propionic acid

5 The title compound was prepared from 3-(4-hydroxypheny1)-2-methy1-2-(4-trifluoromethoxy-phenoxy)-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester using the procedure of Example 42. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, 10 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 8.4 Hz), 6.90 (d, 2H, J =8.4 Hz), 6.79 (d, 2H, J = 8.4 Hz), 4.43 (bs, 1H), 4.16 (t,2H, J = 6.0 Hz), 3.25 and 3.13 (d of Abq, 2H, J = 14.0 Hz), 3.02 (t, 2H, J = 6.0 Hz), 3.02-2.98 (m, 1H), 2.36 (s, 3H), 2.09-2.00 (m, 2H), 1.88-1.79 (m, 2H), 1.78-1.69 (m, 1H), 1.64-1.52 (m, 2H), 1.43 (s, 3H), 1.40-1.23 (m, 3H). IR 15 (KBr) 3600, 2980, 1725, 1601, 1500, 1268 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for $C_{29}H_{33}NO_6F_3$ 548.2260, found 548.2274.

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Example 45

2-Methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-2-(4-trifluoromethoxy-phenoxy)-propionic acid

5

The title compound was prepared from 3-(4-hydroxy-pheny1)-2-methy1-2-(4-trifluoromethoxy-phenoxy)-propionic acid ethy1 ester and toluene-4-sulfonic acid 2-(5-methy1-2-(1-methy1cyclohexy1)oxazol-4-y1)-ethy1 ester using the

10 procedure of Example 42. ¹H NMR (400 MHz, CDCl₃) δ 7.16 (d, 2H, J = 8.60 Hz), 7.08 (d, 2H, J = 8.60 Hz), 6.89 (d, 2H, J = 8.60 Hz), 6.79 (d, 2H, J = 8.60 Hz), 4.13 (t, 2H, J = 6.25 Hz), 3.23 (d, 1H, J = 14.08 Hz), 3.11 (d, 1H, J = 14.08 Hz), 2.99 (t, 2H, J = 6.25 Hz), 2.33 (s, 3H), 2.16-2.08 (m, 2H), 1.62-1.32 (m, 8H), 1.42 (s, 3H), 1.32 (s, 3H); MS (ES⁺) calcd for C₃₀H₃₅NO₆F₃: Found m/e 562.3 (M + 1, 100%)

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Example 46

2-{4-[2-(5-Methy1-2-pheny1-oxazo1-4-y1)-ethoxy]-benzy1}-2-phenoxy-butyric acid

The Standard Procedure (B) was utilized to prepare the title compound from 2-(4-hydroxybenzyl)-2-phenoxybutyric acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 7.99-7.94 (m, 2H), 7.44-7.40 (m, 3H), 7.32-7.28 (m, 2H), 7.07 (t, 1H, J = 7.4 Hz), 7.02-6.97 (m, 4H), 6.79-6.74 (m, 2H), 4.18 (t, 2H, J = 6.6 Hz), 3.29 (s, 2H), 2.98 (t, 2H, J = 6.6 Hz), 2.37 (s, 3H), 2.14 (qd, 1H, J = 14.8, 7.6 Hz), 2.07 (qd, 1H, J = 14.8, 7.6 Hz), 0.91 (t, 3H, J = 7.6 Hz).

Example 47

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2-{4-[2-(5-Methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-benzyl}-2-phenoxy-butyric acid

The title compound was prepared from 2-(4-

20 hydroxybenzyl)-2-phenoxybutyric acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-

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4-yl)-ethyl ester using the method of Example 46. H NMR $(400 \text{ MHz}, \text{CDCl}_3) \delta 7.59 \text{ (dd, 1H, J = 3.6, 0.8 Hz), 7.37 (dd, }$ 1H, J = 5.2, 1.2 Hz), 7.33-7.27 (m, 2H), 7.09-7.05 (m, 2H), 7.02-6.96 (m, 4H), 6.78-6.73 (m, 2H), 4.16 (t, 2H, J = 6.6Hz), 3.29 (s, 2H), 2.94 (t, 2H, J = 6.6 Hz), 2.34 (s, 3H), 2.14 (qd, 1H, J = 14.8, 7.6 Hz), 2.07 (qd, 1H, J = 14.8, 7.6)Hz), 0.91 (t, 3H, J = 7.6 Hz).

Example 48

{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-benzyl}-10 2-phenoxy-butyric acid

The title compound was prepared from 2-(4hydroxybenzyl)-2-phenoxybutyric acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-15 yl)-ethyl ester using the method of Example 46. ¹H NMR (400 MHz, CDCl₃) δ 8.01(bs, 1H), 7.31-7.26 (m, 2H), 7.06-6.96 (m, 5H), 6.72 (d, 2H, J = 8.8 Hz), 4.08 (t, 2H, J = 6.4 Hz), 3.28 (s, 2H), 2.91 (t, 2H, J = 6.4 Hz), 2.81 (tt, 1H, J =20 11.6, 3.6 Hz), 2.26 (s, 3H), 2.18-1,98 (m, 4H), 1.82-1.77 (m, 2H), 1.72-1.67 (m, 1H), 1.58-1.48 (m, 2H), 1.39-1.18 (m, 3H), 0.92 (t, 3H, J = 7.6 Hz).

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Example 49

2-(4-{2-[5-Methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-benzyl)-2-phenoxy-butyric acid

The title compound was prepared from 2-(4-hydroxybenzyl)-2-phenoxybutyric acid ethyl ester and toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl) oxazol-4-yl)-ethyl ester using the method of Example 46. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (dd, 2H, J = 8.60 Hz, J = 7.43 ld, 7.07-7.03 (m, 1H), 7.02-6.96 (m, 4H), 6.72 (d, 2H, J = 8.60 Hz), 4.10 (t, 2H, J = 6.25 Hz), 2.38 (s, 2H), 2.95 (t, 2H, J = 6.25 Hz), 2.29 (s, 3H), 2.15-2.01 (m, 4H), 1.56-1.36 (m, 8H), 1.30 (s, 3H), 0.91 (t, 3H, J = 7.43 Hz); MS (ES⁺) calcd for C₃₀H₃₈NO₅: Found m/e 492.3 (M + 1, 100%).

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Example 50

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-trifluoromethyl-phenoxy)-propionic acid

5 Standard Procedure (B) was utilized to prepare the title compound from 3-(4-hydroxyphenyl)-2-methyl-2-(4-trifluoromethyl-phenoxy)-propionic acid ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 9.18 (bs, 1H), 7.96 (d, 2H, J = 6.8 Hz), 7.52-7.40 (m, 5H), 7.16 (d, 2H, J = 8.4 Hz), 6.93 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.4 Hz), 4.18 (t, 2H, J = 6.0 Hz), 3.28 and 3.15 (d of Abq, 2H, J = 14.0 Hz), 3.05 (t, 2H, J = 6.0 Hz), 2.42 (s, 3H), 1.47 (s, 3H). IR (KBr) 3420, 1734, 1613, 1513, 1328 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for C₂₉H₂₇NO₅F₃ 526.1841, found 526.1851.

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Example 51

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-trifluoromethyl-phenoxy)-propionic acid

5 The title compound was prepared from 3-(4hydroxyphenyl)-2-methyl-2-(4-trifluoromethyl-phenoxy)propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester using the procedure of Example 50. 1 H NMR (400 MHz, CDCl₃) δ 8.67 (bs, 1H), 7.66 (d, 1H, J = 3.2 Hz), 7.48 (d, 2H, J = 8.4 Hz), 10 7.43 (d, 1H, J = 5.0 Hz), 7.16 (d, 2H, J = 8.4 Hz), 7.08 (dd, 1H, J = 5.0, 3.2 Hz), 6.95 (d, 2H, J = 8.4 Hz), 6.80(d, 2H, J = 8.4 Hz), 4.16 (t, 2H, J = 6.2 Hz), 3.28 and 3.16(d of Abq, 2H, J = 13.8 Hz), 3.00 (t, 2H, J = 6.2 Hz), 2.37 (s, 3H), 1.49 (s, 3H). IR (KBr) 3420, 3000, 1714, 1614, 15 1513, 1327 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for $C_{27}H_{25}NO_5F_3S$ 532.1406, found 532.1412.

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Example 52

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-(4-trifluoromethyl-phenoxy)-propionic acid

The title compound was prepared from 3-(4-5 hydroxyphenyl) -2-methyl-2-(4-trifluoromethyl-phenoxy) propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester using the procedure of Example 50. 1 H NMR (400 MHz, CDCl₃) δ 7.48 (d, 2H, J = 8.8 Hz), 7.16 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J =10 8.4 Hz), 6.78 (d, 2H, J = 8.4 Hz), 4.11 (t, 2H, J = 6.2 Hz), 3.24 and 3.15 (d of ABq, 2H, J = 13.8 Hz), 2.95 (t, 2H, J =6.2 Hz), 2.85 (tt, 1H, J = 11.6, 3.4 Hz), 2.30 (s, 3H), 2.03-1.95 (m, 2H), 1.83-1.74 (m, 2H), 1.73-1.68 (m, 1H), 1.58-1.47 (m, 1H), 1.49 (s, 3H), 1.38-1.17 (m, 4H). IR 15 (KBr) 3400, 2937, 1735, 1614, 1513, 1328 cm⁻¹. HRMS (ES⁺) m/z exact mass calcd for $C_{29}H_{33}NO_5F_3$ 532.2311, found 532.2332.

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Example 53

2-Methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-2-(4-trifluoromethyl-phenoxy)-propionic acid

5

The title compound was prepared from 3-(4-hydroxyphenyl)-2-methyl-2-(4-trifluoromethyl-phenoxy)propionic acid ethyl ester and toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl)-ethyl ester using

10 the procedure of Example 50. ¹H NMR (400 MHz, CDCl₃) δ 7.49
(d, 2H, J = 8.60 Hz), 7.15 (d, 2H, J = 8.60 Hz), 6.94 (d, 2H, J = 8.60 Hz), 6.78 (d, 2H, J = 8.60 Hz), 4.13 (t, 2H, J = 6.25 Hz), 3.25 (d, 1H, J = 14.08 Hz), 3.15 (d, 1H, J = 14.08 Hz), 2.99 (t, 2H, J = 6.25 Hz), 2.33 (s, 3H), 2.14
15 2.06 (m, 2H), 1.61-1.41 (m, 8H), 1.49 (s, 3H), 1.30 (s, 3H); MS (ES⁺) calcd for C₃₀H₃₅NO₅F₃: Found m/e 546.3 (M + 1, 100%).

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Example 54

(S)-3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-(4-trifluoromethyl-phenoxy)-propionic acid

5

10

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The title compound was prepared from (S)-3-(4-hydroxyphenyl)-2-methyl-2-(4-trifluoromethyl-phenoxy)-propionic acid ethyl ester (95% ee; Chiralpak AD separation, 8 x 27 cm, 10% IPA/heptane, 275 nm) and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester by the procedure described in Example 1.

Example 55

(S)-2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-trifluoromethyl-phenoxy)-propionic acid

The title compound was prepared from (S)-3-(4-hydroxyphenyl)-2-methyl-2-(4-trifluoromethyl-phenoxy)-propionic acid ethyl ester (95% ee; Chiralpak AD separation,

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8 x 27 cm, 10% IPA/heptane, 275 nm) and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester by the procedure described in Example 1.

Example 56

5

2-(3,4-Difluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

Standard Procedure (B) was utilized to prepare 2-(3,4-10 difluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid from 2-(3,4-difluoro-phenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 9.13 (bs, 1H), 7.99-7.95 (m, 2H), 7.48-7.41 (m, 3H), 7.17 (d, 2H, J = 8.4 Hz), 6.99 (q, 1H, J = 9.5 Hz), 6.82 (d, 2H, J = 8.4 Hz), 6.75 (ddd, 1H, J = 11.6, 6.4, 2.8 Hz), 6.63-6.56 (m, 1H), 4.20 (t, 2H, J = 6.4 Hz), 3.22 and 3.10 (d of ABq, 2H, J = 13.8 Hz), 3.04 (t, 2H, J = 6.4 Hz), 2.41 (s, 3H), 1.38 (s, 3H).

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Example 57

2-(3,4-Difluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared from 2-(3,4-difluoro-phenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester using the method of Example 56.

¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, d, 1H, J = 3.6 Hz), 7.39

10 (d, 1H, J = 5.2 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.08 (dd, 1H, J = 5.2, 3.6 Hz), 7.00 (q, 1H, J = 9.5 Hz), 6.82 (d, 2H, J = 8.4 Hz), 6.78 (ddd, 1H, J = 11.6, 6.4, 2.8 Hz), 6.65-6.60 (m, 1H), 4.18 (t, 2H, J = 6.4 Hz), 3.22 and 3.12 (d of ABq, 2H, J = 13.6 Hz), 2.98 (t, 2H, J = 6.4 Hz), 2.37 (s, 3H), 1.40 (s, 3H).

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Example 58

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl)-2-(3,4-difluoro-phenoxy)-2-methyl-propionic acid

The title compound was prepared from 2-(3,4-difluoro-phenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester using the method of Example 56. ¹H NMR (400 MHz, CDCl₃) δ 9.37 (bs, 1H), 7.16 (d, 2H, J = 8.4 10 Hz), 6.99 (dd, 1H, J = 9.5 Hz), 6.78 (d, 2H, J = 8.4 Hz), 6.77-6.72 (m, 1H), 6.63-6.58 (m, 1H), 4.12 (t, 2H, J = 6.4 Hz), 3.21 and 3.08 (d of ABq, 2H, J = 14.0 Hz), 2.97 (t, 2H, J = 6.4 Hz), 2.91 (tt, 1H, J = 12.0, 3.6 Hz), 2.32 (s, 3H), 2.04-1.98 (m, 2H), 1.85-1.78 (m, 2H), 1.76-1.68 (m, 1H), 1.62-1.49 (m, 2H), 1.41-1.19 (m, 3H), 1.37 (s, 3H).

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Example 59

2-(3,4-Difluoro-phenoxy)-2-methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid

5

The title compound was prepared from 2-(3,4-difluoro-phenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl)-ethyl ester using the method of Example 56. ¹H NMR (400 MHz, CDCl₃) δ 7.15 (d, 2H, J = 8.60 Hz), 7.00 (q, 1H, J = 8.99 Hz), 6.79 (d, 2H, J = 8.60 Hz), 6.77-6.74 (m, 1H), 6.63-6.61 (m, 1H), 4.12 (t, 2H, J = 6.25Hz), 3.19 (d, 1H, J = 14.08 Hz), 3.09 (d, 1H, J = 14.08 Hz), 2.97 (t, 2H, J = 6.25 Hz), 2.31 (s, 3H), 2.16-2.08 (m, 2H), 1.61-1.35 (m, 8H), 1.39 (s, 3H), 1.29 (s, 3H); MS (ES⁺) calcd for C₂₉H₃₄NO₅F₂: Found m/e 514.3 (M + 1, 100%).

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Example 60

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]phenyl}-2-m-tolyloxy-propionic acid

The title compound was prepared from 3-(4-hydroxy-phenyl)-2-methyl-2-m-tolyloxy-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester using Standard Procedure (B). ¹H NMR (400 MHz, CDCl₃) δ 8.04-8.01 (m, 2H), 7.47-7.45 (m, 3H), 7.18 (d, 2H, J = 8.60 Hz), 7.13 (t, 1H, J = 7.82 Hz), 6.87-6.85 (m, 1H), 6.82 (d, 2H, J = 8.60 Hz), 6.74-6.67 (m, 2H), 4.23 (t, 2H, J = 6.26 Hz), 3.24 (d, 1H, J = 13.69 Hz), 3.12 (d, 1H, J = 13.69 Hz), 3.06 (t, 2H, J = 6.26 Hz), 2.41 (s, 3H), 2.29 (s, 3H), 1.42 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₉H₃₀NO₅ 472.2124, found 472.2098.

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Example 61

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-m-tolyloxy-propionic acid

The title compound was prepared from 3-(4-hydroxyphenyl)-2-methyl-2-m-tolyloxy-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester using the procedure of Example 60. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, 1H, J = 3.52 Hz), 7.46 (d, 1H, J = 4.69 Hz), 7.17 (d, 2H, J = 8.21 Hz), 7.16-7.10 (m, 2H), 6.87-6.86 (m, 1H), 6.81 (d, 2H, J = 8.60 Hz), 6.72-6.69 (m, 2H), 4.21 (t, 2H, J = 6.26 Hz), 3.24 (d, 1H, J = 14.08 Hz), 3.12 (d, 1H, J = 14.08 Hz), 3.01 (t, 2H, J = 6.26 Hz), 2.38 (s, 3H), 2.30 (s, 3H), 1.41 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₇H₂₈NO₅S 478.1688, found 478.1692.

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Example 62

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-m-tolyloxy-propionic acid

The title compound was prepared from 3-(4-hydroxyphenyl)-2-methyl-2-m-tolyloxy-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester using the procedure of Example 60.

¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, 2H, J = 8.60 Hz), 7.13 (t, 1H, J = 7.82 Hz), 6.85 (d, 1H, J = 7.43 Hz), 6.78 (d, 2H, J = 8.60 Hz), 6.69-6.68 (m, 2H), 4.16 (t, 2H, J = 5.86 Hz), 3.20 (d, 1H, J = 14.08 Hz), 3.14 (d, 1H, J = 14.08 Hz), 3.09-2.96 (m, 3H), 2.33 (s, 3H), 2.30 (s, 3H), 2.06-2.02 (m, 2H), 1.83-1.80 (m, 2H), 1.73-1.70 (m, 1H), 1.59-1.56 (m, 2H), 1.41 (s, 3H), 1.38-1.26 (m, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₉H₃₆NO₅ 478.2593, found 478.2592.

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Example 63

2-(4-Fluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

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Example 64

2-(4-Fluoro-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared from 2-(4-fluorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester using the procedure of Example 63. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, 1H, J = 3.52 Hz, J = 1.17 Hz), 7.36 (dd, 1H, J = 5.08 Hz, J = 1.17 Hz), 7.18 (d, 2H, J = 8.60 Hz), 7.06 (dd, 1H, J = 5.08 Hz, J = 3.91 Hz), 6.93-6.85 (m, 4H), 6.82 (d, 2H, J = 8.60 Hz), 4.18 (t, 2H, J = 6.65 Hz), 3.21 (d, 1H, J = 13.69 Hz), 3.13 (d, 1H, J = 13.69 Hz), 2.96 (t, 2H, J = 6.65 Hz), 2.35 (s, 3H), 1.36 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₆H₂₅NO₅FS 482.1437, found 482.1451.

Example 65

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(4-fluoro-phenoxy)-2-methyl-propionic acid

The title compound was prepared from 2-(4-fluorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester using the procedure of Example 63. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, 2H, J = 8.60 Hz), 6.95-6.85 (m, 4H), 6.79 (d, 2H, J = 8.60 Hz), 4.12 (t, 2H, J = 6.26 Hz), 3.20 (d, 1H, J = 14.08 Hz), 3.11 (d, 1H, J = 14.08 Hz), 2.95 (t, 2H, J = 6.26 Hz) 2.85 (tt, 1H, J = 11.73 Hz, J = 3.52 Hz), 2.30 (s, 3H), 2.02-1.99 (m, 2H), 1.83-1.78 (m, 2H), 1.72-1.69 (m, 1H), 1.58-1.49 (m, 2H), 1.36 (s, 3H), 1.33-1.22 (m, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₈H₃₃NO₅F 482.2343, found 482.2347.

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Example 66

2-(4-Fluoro-phenoxy)-2-methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl}-ethoxy}-phenyl)-propionic acid

The title compound was prepared from 2-(4-fluorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl)-ethyl ester using the procedure of Example 63. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (d, 2H, J = 8.60 Hz), 6.93-6.84 (m, 4H), 6.69 (d, 2H, J = 8.60 Hz), 4.13 (t, 2H, J = 6.06 Hz), 3.22 (d, 1H, J = 13.68 Hz), 3.09 (d, 1H, J = 13.68 Hz), 2.98 (t, 2H, J = 6.06 Hz), 2.31 (s, 3H), 2.17-2.09 (m, 2H), 1.57-1.50 (m, 4H), 1.45-1.37 (m, 4H), 1.35 (s, 3H), 1.31 (s, 3H); MS (ES⁺) calcd for
15 C₂₉H₃₅NO₅F: Found m/e 496.3 (M + 1, 100%).

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Example 67.

(S) -2-(4-Fluoro-phenoxy) -2-methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid

5

The title compound was prepared from (S)-2-(4-fluorophenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)-oxazol-4-yl)-ethyl ester (95% ee;

10 Chiralpak AD separation, 8 x 28 cm, 10% IPA/heptane, 275 nm) by the procedure described in Example 1.

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Example 68

(S)-2-(4-Methanesulfonyl-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

Standard Procedure(B) was utilized to prepare the title compound from 3-(4-hydroxypheny1)-2-(4-methanesulfony1-phenoxy)-2-methy1-propionic acid ethy1 ester and toluene-4-sulfonic acid 2-(2-pheny1-5-methy1-oxazol-4-y1)-ethy1 ester.

¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, 2H, J = 7.04 Hz), 7.80 (d, 2H, J = 9.00 Hz), 7.55-7.50 (m, 3H), 7.14 (d, 2H, J = 8.60 Hz), 6.97 (d, 2H, J = 9.00 Hz), 6.80 (d, 2H, J = 8.21 Hz), 4.20 (t, 2H, J = 5.87 Hz), 3.29 (d, 1H, J = 14.08 Hz), 3.17 (d, 1H, J = 14.08 Hz), 3.10 (t, 2H, J = 5.87 Hz) 3.01 (s, 3H), 2.46 (s, 3H), 1.54 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₉H₃₀NO₇S 536.1743, found 536.1771.

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Example 69

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]phenyl}-2-(4-nitro-phenoxy)-propionic acid

5 Standard Procedure (B) was utilized to prepare the title compound from toluene-4-sulfonic acid 2-(2-pheny1-5-methy1-oxazol-4-y1)-ethy1 ester. ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, 2H, J = 9.00 Hz), 8.05-7.96 (m, 2H), 7.52-7.45 (m, 3H), 7.14 (d, 2H, J = 8.60 Hz), 6.90 (d, 2H, J = 9.00 Hz), 6.80 (d, 2H, J = 8.60 Hz), 4.20 (t, 2H, J = 5.87 Hz), 3.29 (d, 1H, J = 14.08 Hz), 3.18 (d, 1H, J = 14.08 Hz), 3.08 (t, 2H, J = 5.87 Hz), 2.45 (s, 3H), 1.55 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₈H₂₇N₂O₇ 503.1818, found 503.1850.

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Example 70

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-trifluoromethyl-phenoxy)-propionic acid

5 Standard Procedure (B) was utilized to prepare the title compound from 3-(4-hydroxy-pheny1)-2-methy1-2-(3-trifluoromethyl-phenoxy)-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-y1)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 7.99-7.97 (m, 2H), 7.50-7.46 (m, 3H), 7.33 (t, 1H, J = 8.21 Hz), 7.26-7.24 (m, 1H), 7.17 (d, 2H, J = 8.60 Hz), 7.14-7.12 (m, 1H), 7.04-7.01 (m, 1H), 6.81 (d, 2H, J = 8.60 Hz), 4.20 (t, 2H, J = 5.87 Hz), 3.27 (d, 1H, J = 14.08 Hz), 3.14 (d, 1H, J = 14.08 Hz), 3.07 (t, 2H, J = 5.87 Hz), 2.42 (s, 3H), 1.44 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₉H₂₇NO₅F₃ 526.1841, found 526.1845.

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Example 71

2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-(3-trifluoromethyl-phenoxy)-propionic acid

The title compound was prepared from 3-(4-hydroxy-phenyl)-2-methyl-2-(3-trifluoromethyl-phenoxy)-propionic acid ethyl ester using the procedure of Example 70.
¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, 1H, J = 3.51 Hz), 7.47 (d, 1H, J = 5.08 Hz), 7.35 (t, 1H, J = 8.01 Hz), 7.29-7.27 (m, 1H), 7.19-7.11 (m, 4H), 7.08-7.03 (m, 1H), 6.82 (d, 2H, J = 8.60 Hz), 4.18 (t, 2H, J = 6.26 Hz), 3.27 (d, 1H, J = 14.08 Hz), 3.15 (d, 1H, J = 14.08 Hz), 3.02 (t, 2H, J = 6.26 Hz), 2.39 (s, 3H), 1.46 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₇H₂₅NO₅F₃S 532.1405, found 532.1423.

15

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Example 72

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-(3-trifluoromethyl-phenoxy)-propionic acid

The title compound was prepared from 3-(4-hydroxy-pheny1)-2-methy1-2-(3-trifluoromethy1-phenoxy)-propionic acid ethyl ester using the procedure of Example 70.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (t, 1H, J = 7.82 Hz), 7.28-7.26 (m, 1H), 7.16 (d, 2H, J = 8.60 Hz), 7.13-7.12 (m, 1H), 7.05-7.02 (m, 1H), 6.78 (d, 2H, J = 8.60 Hz), 4.14 (t, 2H, J = 5.67 Hz), 3.26 (d, 1H, J = 14.08 Hz), 3.13 (d, 1H, J = 14.08 Hz), 3.01-2.93 (m, 3H) 2.35 (s, 3H), 2.05-2.01 (m, 2H), 1.83-1.78 (m, 2H), 1.73-1.69 (m, 1H), 1.58-1.49 (m, 2H), 1.45 (s, 3H), 1.37-1.18 (m, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₉H₃₃NO₅F₃ 532.2311, found 532.2305.

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Example 73

2-Methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-2-(3-trifluoromethyl-phenoxy)-propionic acid

5

Standard Procedure (B) was utilized to prepare the title compound from toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl)ethyl ester. 1 H NMR (400 MHz, CDCl₃) δ 7.34 (t, 1H, J = 8.01 Hz), 7.28-7.26 (m, 1H), 7.16 (d, 2H, J = 8.60 Hz), 7.13-7.13 (m, 1H), 7.06-7.01 (m, 1H), 6.79 (d, 2H, J = 8.60 Hz), 4.14 (t, 2H, J = 6.25 Hz), 3.24 (d, 1H, J = 14.08 Hz), 3.13 (d, 1H, J = 14.08 Hz), 2.99 (t, 2H, J = 6.25 Hz), 2.34 (s, 3H), 2.14-2.08 (m, 2H), 1.62-1.32 (m, 8H), 1.45 (s, 3H), 1.31 (s, 3H); MS (ES⁺) calcd for C₃₀H₃₅NO₅F₃: Found m/e 546.2 (M + 1, 100%).

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Example 74

2-(3-Methoxy-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

Standard Procedure (B) was utilized to prepare the title compound from 3-(4-hydroxy-phenyl)-2-(3-methoxy-phenoxy)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester.

¹H NMR (400 MHz, CDCl₃) δ 7.97-7.95 (m, 2H), 7.42-7.39 (m, 3H), 7.18-7.12 (m, 3H), 6.83 (d, 2H, J = 8.99 Hz), 6.61-6.58 (m, 1H), 6.52-6.46 (m, 2H), 4.21 (t, 2H, J = 6.65 Hz), 3.74 (s, 3H), 3.25 (d, 1H, J = 13.69 Hz), 3.15 (d, 1H, J = 13.69 Hz), 2.98 (t, 2H, J = 6.65 Hz), 2.37 (s, 3H), 1.45 (s, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₉H₃₀NO₆ 488.2073, found 488.2083.

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Example 75

2-(3-Methoxy-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared from 3-(4-hydroxy-pheny1)-2-(3-methoxy-phenoxy)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester using the procedure of Example 74.

1 NMR (400 MHz, CDCl₃) δ 7.58 (d, 1H, J = 3.52 Hz), 7.36 (d, 1H, J = 5.08 Hz), 7.17-7.13 (m, 3H), 7.08-6.99 (m, 1H), 6.82 (d, 2H, J = 8.60 Hz), 6.62-6.59 (m, 1H), 6.52-6.46 (m, 2H), 4.19 (t, 2H, J = 6.65 Hz), 3.75 (s, 3H), 3.24 (d, 1H, J = 14.08 Hz), 3.16 (d, 1H, J = 14.08 Hz), 2.95 (t, 2H, J = 6.65 Hz), 2.35 (s, 3H), 1.45 (s, 3H); HRMS (ES[†]) m/z exact mass calcd for C₂₇H₂₈NO₆S 494.1637, found 494.1642.

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Example 76

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-(3-methoxy-phenoxy)-2-methyl-propionic acid

The title compound was prepared from 3-(4-hydroxy-phenyl)-2-(3-methoxy-phenoxy)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester using the procedure of Example 74.

¹H NMR (400 MHz, CDCl₃) δ 7.17-7.12 (m, 3H), 6.77 (d, 2H, J = 8.99 Hz), 6.61-6.59 (m, 1H), 6.50-6.47 (m, 1H), 6.46 (t, 1H, J = 2.35 Hz), 4.14 (t, 2H, J = 6.06 Hz), 3.75 (s, 3H), 3.25 (d, 1H, J = 14.08 Hz), 3.13 (d, 1H, J = 14.08 Hz), 3.00-2.94 (m, 3H), 2.33 (s, 3H), 2.05-2.01 (m, 2H), 1.83-1.80 (m, 2H), 1.75-1.69 (m, 1H), 1.58-1.54 (m, 2H), 1.44 (s, 3H), 1.37-1.26 (m, 3H); HRMS (ES⁺) m/z exact mass calcd for C₂₉H₃₆NO₆ 494.2543, found 494.2543.

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Example 77

2-(3-Methoxy-phenoxy)-2-methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-propionic acid

5

The title compound was prepared from 3-(4-hydroxy-pheny1)-2-(3-methoxy-phenoxy)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl)-ethyl ester using the

10 procedure of Example 74.

1 NMR (400 MHz, CDCl₃) & 7.16-7.13 (m, 3H), 6.79 (d, 2H, J = 8.60 Hz), 6.61-6.59 (m, 1H), 6.51-6.48 (m, 1H), 6.46 (t, 1H, J = 2.35 Hz), 4.13 (t, 2H, J = 6.25 Hz), 3.75 (s, 3H), 3.24 (d, 1H, J = 13.68 Hz), 3.12 (d, 1H, J = 13.68 Hz), 2.96 (t, 2H, J = 6.25 Hz), 2.30 (s, 3H), 2.15-2.08 (m, 2H), 1.61-1.45 (m, 5H), 1.44 (s, 3H), 1.43-1.36 (m, 3H), 1.30 (s, 3H); MS (ES⁺) calcd for C₃₀H₃₀NO₆: Found m/e 508.3 (M + 1, 100%).

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Example 78

2-(Benzo[1,3]dioxol-5-yloxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

5 Standard Procedure (B) was utilized to prepare the title compound from 2-(benzo[1,3]dioxol-5-yloxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester.

1 NMR (400 MHz, CDCl₃) δ 7.96-7.93 (m, 2H),

10 7.44-7.41 (m, 3H), 7.13 (d, 2H, J = 8.79 Hz), 6.78 (d, 2H, J = 8.79 Hz), 6.60 (d, 1H, J = 8.79 Hz), 6.41 (d, 1H, J = 2.44 Hz), 6.32 (dd, 1H, J = 8.79 Hz, J = 2.44 Hz), 5.88 (d, 2H, J = 0.98 Hz), 4.17 (t, 2H, J = 6.35 Hz), 3.15 (d, 1H, J = 14.16 Hz), 3.04-3.00 (m, 3H), 2.38 (s, 3H), 1.30 (s, 3H);

15 HRMS (ES⁺) m/z exact mass calcd for C₂₉H₂₈NO₇ 502.1866, found 502.1881.

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Example 79

2-(Benzo[1,3]dioxol-5-yloxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared from 2-5 (benzo[1,3]dioxol-5-yloxy)-3-(4-hydroxy-phenyl)-2-methylpropionic acid ethyl ester and toluene-4-sulfonic acid 2-(5methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester using the procedure of Example 78. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, 1H, J = 3.90 Hz, J = 1.47 Hz), 7.35 (dd, 1H, J = 5.37 Hz, J10 = 1.47 Hz), 7.13 (d, 2H, J = 8.31 Hz), 7.04 (dd, 1H, J = 5.37 Hz, J = 3.90 Hz), 6.78 (d, 2H, J = 8.79 Hz), 6.60 (d,1H, J = 8.30 Hz), 6.42 (d, 1H, J = 2.44 Hz), 6.33 (dd, 1H, J= 8.31 Hz, J = 2.44 Hz), 5.88 (d, 2H, J = 0.98 Hz), 4.15 (t, 2H, 3Hz)15 2H, J = 6.35 Hz), 3.16 (d, 1H, J = 13.92 Hz), <math>3.04 (d, 1H, J)= 13.92 Hz), 2.93 (t, 2H, J = 6.35 Hz), 2.31 (s, 3H), 1.30 (s, 3H); HRMS (ES †) m/z exact mass calcd for $C_{27}H_{26}NO_7S$ 508.1430, found 508.1425.

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Example 80

2-(Benzo[1,3]dioxol-5-yloxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid

5 The title compound was prepared from 2-(benzo[1,3] dioxol-5-yloxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5methyl-oxazol-4-yl)-ethyl ester using the procedure of Example 78. ¹H NMR (400 MHz, CDCl₃) δ 7.13 (d, 2H, J = 8.30 10 Hz), 6.75 (d, 2H, J = 8.79 Hz), 6.61 (d, 2H, J = 8.30 Hz), 6.42 (d, 2H, J = 2.44 Hz), 6.33 (dd, 1H, J = 8.30, J = 2.44Hz), 5.88 (d, 2H, J = 0.98 Hz), 4.11 (t, 2H, J = 5.86 Hz), 3.15 (d, 1H, J = 13.68 Hz), 3.03 (d, 1H, J = 13.68 Hz), 2.93(t, 2H, J = 5.86 Hz), 2.86 (tt, 1H, J = 11.72 Hz, J = 3.42)Hz), 2.27 (s, 3H), 1.99-1.96 (m, 2H), 1.80-1.75 (m, 2H), 1.71-1.65 (m, 1H), 1.57-1.46 (m, 2H), 1.37-1.33 (m, 1H), 1.32 (s, 3H), 1.29-1.19 (m, 2H); HRMS (ES †) m/z exact mass calcd for $C_{29}H_{34}NO_7$ 508.2335, found 508.2351.

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Example 81

2-(Benzo[1,3]dioxol-5-yloxy)-2-methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl}-ethoxy}-phenyl)-propionic acid

5

The title compound was prepared from 2-(benzo[1,3] dioxol-5-yloxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-[5-methyl-2-(1-methylcyclohexyl)oxazol-4-yl]-ethyl ester using the

10 procedure of Example 78.

1 NMR (400 MHz, CDCl₃) δ 7.17 (d, 2H, J = 8.60 Hz), 6.65 (d, 1H, J = 8.21 Hz), 6.47 (d, 1H, J = 2.35 Hz), 6.37 (dd, 1H, J = 8.21 Hz, J = 2.35 Hz), 5.92 (d, 2H, J = 0.78 Hz), 4.14 (t, 2H, J = 6.25 Hz), 3.19 (d, 1H, J = 14.08 Hz), 3.07 (d, 1H, J = 14.08 Hz), 2.98 (t, 2H, J = 6.25 Hz), 2.31 (s, 3H), 2.17-2.08 (m, 2H), 1.62-1.35 (m, 8H), 1.34 (s, 3H), 1.31 (s, 3H); MS (ES⁺) calcd for C₃₀H₃₅NO₇: Found m/e 522.3 (M + 1, 100%).

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Example 82

2-{4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzyl}-2-phenoxy-hexanoic acid

5 Standard Procedure (B) was utilized to prepare the title compound from 2-(4-hydroxybenzyl)-2-phenoxy-hexanoic acid ethyl ester and toluene-4-sulfonic acid 2-(2-phenyl-5-methyl-oxazol-4-yl)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 7.97-7.94 (m, 2H), 7.42-7.40 (m, 3H), 7.31-7.27 (m, 2H), 7.06 (t, 1H, J = 7.43 Hz), 6.98 (t, 4H, J = 8.99 Hz), 6.75 (d, 2H, J = 8.60 Hz), 4.17 (t, 2H, J = 6.65Hz), 3.29 (s, 2H), 2.96 (t, 2H, J = 6.65 Hz), 2.36 (s, 3H), 2.10-1.98 (m, 2H), 1.42-1.16 (m, 4H), 0.79 (t, 3H, J = 7.04 Hz); MS (ES⁺) calcd for C₃₁H₃₄NO₅: Found m/e 500.2 (M + 1, 100%).

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Example 83

2-{4-[2-(5-Methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-benzyl}-2-phenoxy-hexanoic acid

The title compound was prepared from from 2-(4-hydroxybenzyl)-2-phenoxy-hexanoic acid ethyl ester and what following the procedure of Example 84. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, 1H, J = 3.91 Hz, J = 1.17 Hz), 7.28 (dd, 1H, J = 5.08 Hz, J = 1.17 Hz), 7.21 (dd, 2H, J = 8.60 Hz, J = 7.43), 6.99-6.95 (m, 2H), 6.92-6.87 (m, 4H), 6.66 (d, 2H, J = 8.60 Hz), 4.07 (t, 2H, J = 6.65 Hz), 3.21 (s, 2H), 2.85 (t, 2H, J = 6.65 Hz), 2.26 (s, 3H), 2.02-1.88 (m, 2H), 1.32-1.09 (m, 4H), 0.71 (t, 3H, J = 7.04 Hz); MS (ES⁺) calcd for C₂₉H₃₂NO₅S: Found m/e 506.2 (M + 1, 100%).

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Example 84

2-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-benzyl}2-phenoxy-hexanoic acid

The title compound was prepared from from 2-(4-hydroxybenzyl)-2-phenoxy-hexanoic acid ethyl ester and what following the procedure of Example 82. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (dd, 2H, J = 8.60 Hz, J = 7.43 Hz), 7.06-6.94 (m, 5H), 6.70 (d, 2H, J = 8.60 Hz), 4.09 (t, 2H, J = 5.86 Hz), 3.30 (d, 1H, J = 14.65 Hz), 3.27 (d, 1H, J = 14.65 Hz), 2.95-2.86 (m, 3H), 2.30 (s, 3H), 2.08-1.92 (m, 4H), 1.83-1.79 (m, 2H), 1.72-1.69 (m, 1H), 1.60-1.50 (m, 2H), 1.42-1.18 (m, 7H), 0.71 (t, 3H, J = 7.04 Hz); MS (ES⁺) calcd for C₃₁H₄₀NO₅: Found m/e 506.3 (M + 1, 100%).

15

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Example 85

2-(4-{2-[5-Methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-benzyl)-2-phenoxy-hexanoic acid

The title compound was prepared from from 2-(4-hydroxybenzyl)-2-phenoxy-hexanoic acid ethyl ester and what following the procedure of Example 82. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (t, 2H, J = 8.01 Hz), 7.06 (t, 1H, J = 7.43 Hz), 7.00-6.95 (m, 4H), 6.71 (d, 2H, J = 8.60 Hz), 4.10 (t, 2H, J = 5.86 Hz), 3.28 (s, 2H), 2.96 (t, 2H, J = 5.86 Hz), 2.30 (s, 3H), 2.13-1.95 (m, 4H), 1.62-1.15 (m, 12H), 1.31 (s, 3H), 0.79 (t, 3H, J = 7.04 Hz); MS (ES⁺) calcd for C₃₂H₄₂NO₅: Found m/e 520.3 (M + 1, 100%).

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Example 86

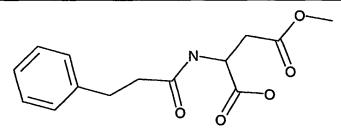
$(S)-2-Methyl-3-\{4-[2-(5-methyl-2-phenethyl-oxazol-4-yl)$ ethoxy]-phenyl}-2-phenoxy-propionic acid

5

20

Step A

2-(3-Phenyl-propionylamino)-succinic acid 4-methyl ester



Methyl L-aspartate (15.0 g, 0.082 mol), DI water (245 mL), acetone (20 mL), and Na_2CO_3 (30.8 g, 0.286 mol) were 10 combined and cooled the solution to 5 °C. 3-Phenyl-propionyl chloride (13.3 mL, 0.089 mol) was added dropwise via addition funnel over 10 min. The reaction was allowed to warm to ambient temperature and stir for 2 h. The reaction became very thick during this time. Added conc. HCl (50 mL) to the slurry until the pH was \leq 4.0. The reaction mixture was extracted with CH2Cl2 (3x). The organic phase was washed with water and then dried (MgSO4), filtered and concentrated under reduced pressure. The clear, colorless oil was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (br s, 1H), 7.28-7.17 (m, 5H), 6.57 (d, J = 7.6 Hz, 1H), 4.87 (m, 1H), 3.67 (s, 3H), 2.96 (t, J = 7.6

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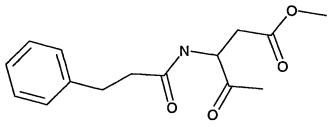
Hz, 2H), 2.89 (A of ABX, J_{AB} = 17.6 Hz, J_{AX} = 4.8 Hz, 1H), 2.88 (B of ABX, J_{BA} = 17.6 Hz, J_{BX} = 4.0 Hz, 1H), 2.69 (t, J = 7.6 Hz, 2H); MS (EI+) 280 (M+H), 302 (M+H+Na).

Step B

5

4-0xo-3-(3-phenyl-propionylamino)-pentanoic acid methyl

<u>ester</u>



2-(3-Phenyl-propionylamino)-succinic acid 4-methyl ester (10 g, 36 mmol), pyridine (50 mL) and acetic anhydride (45 mL) were combined in a 500 mL flask. reaction mixture was heated at 90 °C for 2 h and then cooled to ambient temperature. After concentrating the reaction mixture under reduced pressure, DI water was added (100 mL). (Potential exotherm!). The reaction mixture was partitioned 15 between water and CH2Cl2. The organic phase was washed with 1N HCl and then dried (MgSO₄), filtered and concentrated under reduced pressure. The material was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.20 (m, 5H), 6.79 (br d, J = 7.6 Hz, 1H), 4.72 (X of ABX, 1H), 3.65 20 (s, 3H), 3.01-2.93 (m, 3H), 2.71-2.62 (m, 3H), 2.11 (s, 3H); MS (EI) 278.1 (M+H).

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Step C

(5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid methyl ester

In a 100 mL flask, 4-oxo-3-(3-phenyl-propionylamino)pentanoic acid methyl ester (10 g, 36 mmol), and acetic anhydride (28 mL) were combined. Following addition of concentrated H_2SO_4 (1 mL), the solution was heated to 90 °C for 30 min and then cooled to ambient temperature. The reaction was slowly diluted with DI water (30 mL, potential 10 exotherm). The reaction mixture was partitioned between CH2Cl2 and water. The organic phase was washed with DI water, 10% NaHCO3 (aq), brine (150 mL), and then dried over MgSO4 and concentrated to obtain a brown oil. The residue was purified by column chromatography (600 mL SiO2, 35% 15 EtOAc/hexanes) to provide the desired product (3.25 g) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.20 (m, 5H), 3.72 (s, 3H), 3.47 (s, 2H), 3.08-2.96 (m, 4H), 2.24 (s, 3H); MS (EI+) 260 (M+H).

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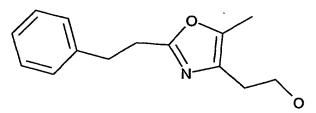
Step D
(5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid

(5-Methyl-2-phenethyl-oxazol-4-yl)-acetic acid methyl ester (8.75 g , 33.8 mmol), in MeOH (120 mL) was treated with 5N NaOH (40 mL) and then the solution was warmed to 40 °C. After 40 min, the reaction mixture was concentrated under reduced pressure, suspended in water, and then acidified to pH=1 with 5N HCl. The mixture was extracted with EtOAc (2x), dried (MgSO₄), and concentrated to provide 5.25 g (63%) of the product as an off-white solid. ¹H NMR (400 MHz, CDCl₃) •• ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.20 (m, 5H), 3.52 (s, 2H), 3.06-3.03 (m, 4H), 2.24 (s, 3H).

Step E

15

2-(5-Methyl-2-phenethyl-oxazol-4-yl)-ethanol



BH₃-THF complex (49 mL of a 1.0 M solution in THF) was added dropwise via addition funnel over 50 min to a solution of (5-methyl-2-phenethyl-oxazol-4-yl)-acetic acid (5.05 g, 20.6 mmol) in THF (35 mL). The reaction mixture was stirred at ambient temperature for 3 h, and then quenched with MeOH (12 mL). After heating at 50 °C for 2 h, the reaction

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mixture was cooled to ambient temperature, and then partitioned between CH_2Cl_2 and 1N NaOH. The organic phase was washed with brine (1x 50 mL), dried over MgSO₄ and concentrated to obtain a residue which was purified by column chromatography (500 mL SiO₂, 35% EtOAc/hexanes) to provide 3.99 g (84%) of the desired product as a clear, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.20 (m, 5H), 3.84 (q, J = 5.6 Hz, 2H), 3.06-2.67 (m, 4H), 2.62 (t, J = 5.6 Hz, 2H), 2.22 (s, 3H); MS (EI+) 232.19 (M+H); 254.15 (M+H+Na).

Step F

Toluene-4-sulfonic acid 2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethyl ester

A solution of 2-(5-methyl-2-phenethyl-oxazol-4-yl)- ethanol (1.2 g, 5.19 mmol) in CH_2Cl_2 at 0°C was treated with pyridine (1.64 g, 20.7 mmol, 1.68 mL), DMAP (190 mg, 1.56 mmol), and tosyl anhyride (2.2 g, 6.75 mmol). The reaction was warmed to ambient temperature and, after 90 min, the solution was filtered through a pad of silica gel (rinsed with CH_2Cl_2). The product was used without further purification. ¹H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.31-7.17 (m, 7H), 4.21 (t, J = 6.8 Hz, 2H), 3.01-2.88 (m, 4H), 2.75 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.19 (s, 3H).

10

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Step G

(S)-2-Methyl-3-{4-[2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxy-propionic acid ethyl ester

(S) -3-(4-Hydroxyphenyl) -2-methyl-2-phenoxypropionic 5 acid ethyl ester (298 mg, 1.0 mmol), toluene-4-sulfonic acid 2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethyl ester (460 mg, 1.19 mmol) and Cs_2CO_3 (388 mg, 1.19 mmol) are combined in anhydrous DMF (8 mL) and stirred for 16 h at 55 °C under an 10 atmosphere of nitrogen. The mixture was then cooled and diluted with ethyl acetate (50 mL), and washed with water then brine. The organic layer was dried with MgSO4 and concentrated in vacuo to a viscous tan oil. The residue was purified by flash column chromatography (200 g silica, 15 hexanes to 25% EtOAc/hexanes) to provide unreacted phenol (80 mg) and the title compound as a colorless oil (340 mg, 67% (91% based on recovered phenol)). H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 9H), 6.98 (tt, J = 7.2, 1.2 Hz, 1H), 6.87-6.83 (m, 4H), 4.22 (q, J = 7.2 Hz, 2H), 4.17 (t, J =6.8 Hz, 2H), 3.29 (A of Abq, J = 14.0 Hz, 1H), 3.13 (B of 20 Abq, J = 14.0 Hz, J = 14.0 Hz, J = 6.8 HzHz, 2H), 2.26 (s, 3H), 1.42 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); MS (EI+) 514.27 (M+H).

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Step H

(S)-2-Methyl-3-{4-[2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxy-propionic acid

5 $(S) - 2 - Methyl - 3 - \{4 - [2 - (5 - methyl - 2 - phenethyl - oxazol - 4 - [2 - (5 - methyl - 2 - phenethyl - 0 - [2 - (5 - methyl - 2 - phenethyl - 0 - [2 - (5 - methyl - 2 - phenethyl - 0 - [2 - (5 - methyl - 2 - phenethyl - 0 - [2 - (5 - methyl - 2 - phenethyl - 0 - [2 - (5 - methyl - 2 - phenethyl - 0 - [2 - (5 - methyl - 2 - [2 - (5 - met$ yl)-ethoxy]-phenyl}-2-phenoxy-propionic acid ethyl ester (340 mg, 0.66 mmol) in MeOH (10 mL) was treated with 2N NaOH (10 mL) and warmed to 55 °C. After 18 h, the mixture was concentrated under reduced pressure and then acidified with 10 5N HCl to pH = 1. The solution was extracted with EtOAc and then the organic phases dried (MgSO₄), filtered and concentrated to a white foam (273 mg, 85%): ¹H NMR (400 MHz, CDCl₃) δ 9.00 (br s, 1H), 7.27-7.15 (m, 9H), 6.95 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.7 Hz, 2H), 6.78 (d, J = 7.7 Hz, 15 2H), 4.10 (t, J = 6.2 Hz, 2H), 3.27 (A of ABq, J = 13.9 Hz, 1H), 3.13 (B of ABq, J = 13.9 Hz, 1H), 3.04 (s, 4H), 2.89 (t, J = 6.2 Hz, 2H), 2.26 (s, 3H), 1.41 (s, 3H); MS (EI+)486.1 (M+H), (EI-) 484.1 (M-H).

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Example 87

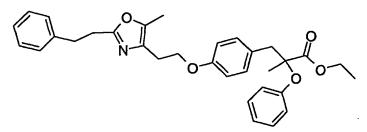
2-Methyl-3-{4-[2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxy-propionic acid

5

WO 02/16331

Step A

2-Methyl-3-{4-[2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxy-propionic acid ethyl ester



Racemic 3-(4-hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester was coupled by the procedure of Example 88, Step G, to provide the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.19 (m, 7H), 7.15 (d, J = 8.4 Hz, 2H), 6.97 (t, J = 7.2, 1H), 6.84-6.81 (m,4 H), 4.21 (q, J = 7.2 Hz, 2H), 4.16 (t, J = 6.8 Hz, 2H), 3.27 (A of Abq, J = 14.0 Hz, 1H), 3.11 (B of Abq, J = 14.0 Hz, 1H), 3.07-2.95 (m, 4H), 2.88 (t, J = 6.8 Hz, 2H), 2.26 (s, 3H), 1.40 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H).

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Step B

2-Methyl-3-{4-[2-(5-methyl-2-phenethyl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxy-propionic acid

The title compound was mage according to the procedure of Example 88, Step H. 1 H NMR (400 MHz, CDCl₃) δ 9.15 (br s, 1H), 7.27-7.08 (m, 9H), 6.89 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 7.7 Hz, 2H), 6.74 (d, J = 7.7 Hz, 2H), 4.07 (t, J = 6.2 Hz, 2H), 3.19 (A of ABq, J = 13.9 Hz, 1H), 3.03 (B of ABq, J = 13.9 Hz, 1H), 3.04-2.96 (m, 4H), 2.84 (t, J = 6.2 Hz, 2H), 2.23 (s, 3H), 1.27 (s, 3H).

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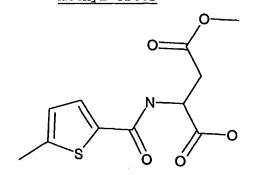
Example 88

(S)-2-(4-{2-[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4yl]-ethoxy}-benzyl)-2-phenoxy-butyric acid

Step A

5

2-[(5-Methyl-thiophene-2-carbonyl)-amino]-succinic acid 4-methyl ester



A mixture of 5-methyl-2-thiophenecarboxylic acid (6.44 g, 45.4 mmol), N-methyl-morpholine (4.82 g, 47.7 mmol), and 2-chloro-4,6-dimethyl-1,3,5-triazine (8.2 g, 46.7 mmol) in THF (100 mL) was stirred at ambient temperature for 90 min. β-Methyl L-aspartate (8.6 g, 46.7 mmol), N-methylmorpholine (9.64 g, 95.3 mmol), and distilled water (10 mL) were added and the mixture was stirred 3 h. The reaction was partitioned between CH₂Cl₂ and 1N HCl. The organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure. The clear, colorless oil was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, J = 3.6 Hz, 1H), 7.09 (br d, J = 7.6 Hz, 1H), 6.74 (dd, J = 3.6, 0.8 Hz,

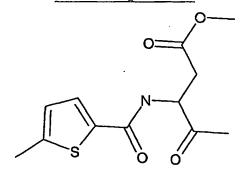
- 172 -

1H), 5.00 (m, 1H), 4.07 (s, 3H), 3.06 (A of ABX, J_{AB} = 17.6 Hz, J_{AX} = 4.4 Hz, 1H), 3.05 (B of ABX, J_{BA} = 17.6 Hz, J_{BX} = 4.8 Hz, 1H), 2.51 (s, 3H).

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Step B

3-[(5-Methyl-thiophene-2-carbonyl)-amino]-4-oxo-pentanoic acid methyl ester



2-[(5-Methyl-thiophene-2-carbonyl)-amino]-succinic acid
4-methyl ester (12 g, 45 mmol), pyridine (60 mL) and acetic
anhydride (50 mL) were combined in a 500 mL flask. The
reaction mixture was heated at 90 °C for 2 h and then cooled
to ambient temperature. After concentrating the reaction
mixture under reduced pressure, DI water was added (100 mL).

(Potential exotherm!). The reaction mixture was partitioned
between water and CH₂Cl₂. The organic phase was washed with
1N HCl and then dried (MgSO₄), filtered and concentrated
under reduced pressure. The material was used without
further purification. MS (EI) 270.1 (M+H).

20

Step C

[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]-acetic acid methyl ester

In a 100 mL flask, 3-[(5-methyl-thiophene-2-25 carbonyl)-amino]-4-oxo-pentanoic acid methyl ester(12 g, 45

- 173 -

mmol), and acetic anhydride (30 mL) were combined. Following addition of concentrated H₂SO₄ (1 mL), the solution was heated to 90 °C for 30 min and then cooled to ambient temperature. The reaction was slowly diluted with DI water (30 mL, potential exotherm). The reaction mixture was partitioned between CH2Cl2 and water. The organic phase was washed with DI water and brine (150 mL), and then dried over MgSO4 and concentrated to obtain a brown oil. The residue was purified by column chromatography (700 mL SiO2, 30% EtOAc/hexanes) to provide the desired product (3.44 g) as a pale yellow oil. Rf=0.39 (50% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, J = 3.6 Hz, 1H), 6.73 (dd, J = 3.6, 0.8 Hz, 1H), 3.71 (s, 3H), 3.55 (s, 2H), 2.51 (s, 3H), 2.32 (s, 3H).

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Step D

[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]-acetic acid

[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]acetic acid methyl ester (3.44 g , 13.7 mmol), in MeOH (45 mL) was treated with 5N NaOH (16 mL) and then the solution was warmed to 40 °C. After 30 min, the reaction mixture was concentrated under reduced pressure, suspended in water, and then acidified to pH=1 with 5N HCl. The mixture was extracted with EtOAc (2x), dried (MgSO₄), and concentrated 25 to provide 2.47 g (76%) of the product as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 3.6 Hz, 1H), 6.73 (dd, J = 3.6, 0.8 Hz, 1H), 3.59 (s, 2H), 2.51 (s, 3H), 2.32 (s, 3H).

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Step E

2-[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]-ethanol

BH3-THF complex (15 mL of a 1.0 M solution in THF) was added dropwise via addition funnel over 50 min to a solution of [5-methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]-acetic acid (1.5 g, 6.33 mmol) in THF (10 mL). The reaction mixture was stirred at ambient temperature for 3 h, and then quenched with MeOH (4 mL). After heating at 50 °C for 2 h, the reaction mixture was cooled to ambient temperature, and then partitioned between CH2Cl2 and 1N NaOH. The organic phase was washed with brine (1x 50 mL), dried over MgSO4 and concentrated to obtain a colorless oil (1.4 g, 99%) which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 3.6 Hz, 1H), 6.73 (dd, J = 3.6, 0.8 15 Hz, 1H), 3.89 (q, J = 5.6 Hz, 2H), 3.04 (t, J = 5.9 Hz, 1H), 2.68 (t, J = 5.6 Hz, 2H), 2.51 (s, 3H), 2.30 (s, 3H); MS (EI+) 224.04 (M+H); 246.06 (M+H+Na).

Step F

20 Toluene-4-sulfonic acid 2-[5-methyl-2-(5-methyl-thiophen-2yl)-oxazol-4-yl]-ethyl ester

A solution of 2-[5-methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]-ethanol(1.42 g, 6.37 mmol) in CH_2Cl_2 (25 mL) at 0°C was treated with pyridine (2.0 g, 25.5 mmol, 2.0 mL), DMAP (233 mg, 1.91 mmol), and tosyl anhyride (2.70 g, 8.28 mmol). The reaction was warmed to ambient temperature and, after 90 min, the solution was filtered through a pad of silica gel (rinsed with CH2Cl2). The product was used without further purification. MS (EI+) 378.1 (M+H).

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Step G

(S)-2-(4-{2-[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]-ethoxy}-benzyl)-2-phenoxy-butyric acid ethyl ester

5 (S)-3-(4-Hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester (255 mg, 0.85 mmol), toluene-4-sulfonic acid 2-[5-methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]ethyl ester (383 mg, 1.02 mmol) and Cs_2CO_3 (335 mg, 1.02 mmol) are combined in anhydrous DMF (6 mL) and stirred for 10 16 h at 55 °C under an atmosphere of nitrogen. The mixture was then cooled and diluted with ethyl acetate (50 mL), and washed with water then brine. The organic layer was dried with MgSO4 and concentrated in vacuo to a viscous tan oil. The residue was purified by flash column chromatography (200 15 g silica, hexanes to 25% EtOAc/hexanes) to provide the title compound as a colorless oil (201 mg, 47%). H NMR (400 MHz, CDCl₃) δ 7.39 (d, J = 3.4 Hz, 1H), 7.22-7.13 (m, 4H), 6.97 (t, J = 7.2 Hz, 1H), 6.85-6.80 (m, 4H), 6.72 (dd, J = 3.6,1.2 Hz, 1H), 4.23-4.17 (m, 4H), 3.26 (A of Abq, J = 13.6 Hz, 20 1H), 3.11 (B of Abq, J = 13.6 Hz, 1H), 2.94 (t, J = 5.6 Hz, 2H), 2.50 (s, 3H), 2.34 (s, 3H), 1.39 (s, 3H), 1.22 (t, J =7.2 Hz, 3H); MS (EI+) 505.9 (M+H); 637.8 (M+H+Cs).

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Step H

(S)-2-(4-{2-[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]-ethoxy}-benzyl)-2-phenoxy-butyric acid

5 . $(S) -2 - (4 - \{2 - [5 - Methyl - 2 - (5 - methyl - thiophen - 2 - yl) - (5 - methyl - yl) - (5 - methyl$ oxazol-4-yl]-ethoxy}-benzyl)-2-phenoxy-butyric acid ethyl ester (201 mg, 0.40 mmol) in MeOH (8 mL) was treated with 2N NaOH (8 mL) and warmed to 55 °C. After 18 h, the mixture was concentrated under reduced pressure and then acidified 10 with 5N HCl to pH = 1. The solution was extracted with EtOAc and then the organic phases dried (MgSO₄), filtered and concentrated to a white foam (158 mg, 81%) that was dried in a vacuum oven at 50 °C for 24 h: 1H NMR (400 MHz, CDCl₃) δ 7.36 (d, J = 3.6 Hz, 1H), 7.16 (t, J = 8.0 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.96 (t, J = 7.2 Hz, 1H), 6.83 (d, J)15 J = 7.6 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 6.71 (dd, J =3.6, 0.8 Hz, 1H), 4.13 (t, J = 6.8 Hz, 2H), 3.18 (A of Abq, J = 13.6 Hz, 1H), 3.00 (B of Abq, J = 13.6 Hz, 1H), 2.90 (t,J = 6.8 Hz, 2H), 2.49 (s, 3H), 2.31 (s, 3H), 1.31 (s, 3H).

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Example 89

2-(4-{2-[5-Methyl-2-(5-methyl-thiophen-2-yl)-oxazol-4-yl]ethoxy}-benzyl)-2-phenoxy butyric acid

The title compound was prepared in the manner of Example 86 from racemic 3-(4-hydroxyphenyl)-2-methyl-2-phenoxypropionic acid ethyl ester and toluene-4-sulfonic acid 2-[5-methyl-2-5-methyl-thiophen-2-yl)-oxazol-4-yl)-ethyl ester. ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, J = 3.2 Hz, 1H), 7.03-6.99 (m, 4H), 6.83 (t, J = 7.2 Hz, 1H), 6.75-6.70 (m, 5H), 4.08 (t, J = 6.4 Hz, 2H), 3.12 (A of Abq, J = 13.6 Hz, 1H), 2.86 (t, J = 6.4 Hz, 2H), 2.81 (B of Abq, J = 13.6 Hz, 1H), 2.48 (s, 3H), 2.27 (s, 3H), 1.12 (s, 3H).

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Example 90

2-Methyl-3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propionyl]thiophen-2-yl}-2-phenoxy-propionic acid

Step A

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3-Hydroxy-2-methyl-2-phenoxy-3-thiophen-2-yl-propionic acid

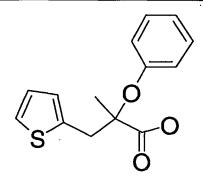
To a 2.0 M solution of LDA in THF/ heptane/ ethyl benzene (200 mL, 408 mmol) cooled by an ice/ acetone bath, a 0.75 M solution of 2-phenoxypropionic acid (30.8 g, 185 mmol) in THF (250 mL) was added dropwise over 30 min, keeping the reaction temperature below -10 °C. After allowing the reaction mixture to stir for 15 min, a 0.75 M solution of 2-thiophenecarboxaldehyde (20.8 g, 185 mmol) in THF (250 mL) was added dropwise over the course of 1 h, maintaining the reaction temperature below -5 °C. After stirring for 5 min at 0 °C, HPLC analysis showed the reaction to be complete. The reaction was poured into ice water (600 mL) and ether (500 mL) was added. Hexane (1.0 L)

- 179 -

was added and the layers were separated. The aqueous layer was further extracted with Et₂O: hexane (1:2) (750 mL). The organic layers were checked for product then discarded. Ethyl acetate (500 mL) was added to the aqueous layer, acidified to pH=2 with conc. HCl (18 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 200 mL). The organic layer was dried over NaCl and solvent removed in vacuo to provide 50.0 g of crude product. The product was used in the next step without further purification: ¹H NMR (400 MHz, CDCl₃) δ 7.33 (dd, 1 H), 7.26 (m, 2 H), 7.12 (m, 1 H), 7.04 (d, 1 H), 6.97 (m, 2 H), 6.87 (dd, 1 H), 5.37 (s, 1 H), 1.40 (s, 3 H); MS (EI-) 277.1 (M -1)⁻.

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Step B
2-Methyl-2-phenoxy-3-thiophen-2-yl-propionic acid



To a solution of triethylsilane (56.4 g, 77.4 mL, 485 mmol) in 100 mL of CH₂Cl₂ at -20 °C, boron trifluoride

20 diethyl etherate (68.8 g, 61.5 mL, 485 mmol) was added. A solution of 3-hydroxy-2-methyl-2-phenoxy-3-thiophen-2-yl-propionic acid (45.0 g, 162 mmol) in CH₂Cl₂ (600 mL) was then added dropwise to the BF₃ solution over 1 h, keeping the temperature at -15 °C. The reaction was stirred at 0 °C for 2 h. The reaction was quenched with 1 N NaOH (approx.

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360 mL) diluted with 180 mL of water and the pH was adjusted to pH=4.0 using 1 N HCl and 1 N NaOH. The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (2 x 300 mL). The combined organic layers were then washed with 0.1 N HCl (300 mL) and water (2 x 300 mL). Xylene (150 mL) and NaCl were added and the organics were concentrated to dryness to yield 40.0 g of crude product. The product was used in the next step without further purification: 1 H NMR (400 MHz, CDCl₃) δ 6.86- 7.29 (m, 8 H), 3.53 (d, 2 H), 3.37 (d, 2 H), 1.44 (s, 3 H); MS (EI) 263.1 (M+H)⁺.

Step C

$\underline{\hbox{2-Methy1-2-phenoxy-3-thiophen-2-yl-propionic acid methy1}}$

15 <u>ester</u>

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In a 100 mL beaker, 1.12 g of 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) was added to a solution of ether (30 mL) and 5 N KOH (2.3 mL) and stirred until N₂ evolution ceased. In another beaker, crude 2-methyl-2-phenoxy-3-thiophen-2-yl-propionic acid (1.00 g) was dissolved in CH2Cl₂ (20 mL). The beaker containing the ether/base mixture was then placed in a Dewar flask containing dry ice/acetone, the aqueous layer was frozen and the ether layer decanted into the other beaker containing the crude acid solution. This mixture was then stirred for an additional 5

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min, which by HPLC showed the reaction to be complete. solvent was removed in vacuo to provide a crude oil. Purification by flash chromatography EtOAc: hexane (1:10) provided 533 mg of desired product (28 %): 1H NMR (400 MHz, CDCl₃) • 7.16-7.22 (m, 4 H), 6.96 (m, 1 H), 6.91 (m, 1 H), 6.84 (m, 2 H), 3.73 (s, 3 H), 3.49 (d, 1 H), 3.38 (d, 1 H), 1.42 (s, 3 H); MS (EI) $277.1 (M+H)^{+}$.

Step D

3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionitrile

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Toluene-4-sulfonic acid 2-(5-methyl-2-phenyloxazol-4yl)ethyl ester (5.00 g, 14.0 mmol), sodium cyanide (852 mg, 16.8 mmol), and potassium bicarbonate (1.70 g, 16.8 mmol) were combined and vigorously stirred in DMSO (50 mL) at 50 °C for 2 h, then overnight at 25 °C. The mixture was then poured into H_2O (50 mL) and extracted with Et_2O (2 x 50 mL). The organic layer were combined then washed with H2O (50 mL), sat. NaCl (50 mL), dried over NaCl. The solvent was removed in vacuo to provide 2.90 g (98%) of product as a 20 white powder: 1 H NMR (400 MHz, CDCl₃) δ 7.93 (m, 2 H), 7.39 (m, 3 H), 2.81 (t, 2 H), 2.71 (t, 2 H), 2.35 (s, 3 H); MS (EI) 213.1 $(M+H)^+$.

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Step E
3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionic acid

A mixture of 3-(5-methyl-2-phenyl-oxazol-4-yl)
propionitrile (3.4 g, 16.0 mmol) and HCl (10 mL) was stirred at 95 °C for 4.5 h. The reaction mixture was cooled to room temperature, poured into ice water (50 mL). The product was extracted with a 1:1 mixture of Et₂O and EtOAc (2 x 50 mL). The combined organic layers were washed with sat. NaCl (50 mL), dried over NaCl, and solvent removed in vacuo to afford 2.27 g (61 %) of acid as a white solid: ¹H NMR (400 MHz, CDCl₃) & 7.93 (m, 2 H), 7.40 (m, 3 H), 2.78 (t, 2 H), 2.76 (t, 2 H), 2.32 (s, 3 H); MS (EI) 232.0 (M+H)⁺.

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Step F

2-Methy1-3-{5-[3-(5-methy1-2-pheny1-oxazo1-4-y1)-propiony1]thiophen-2-y1}-2-phenoxy-propionic acid methy1 ester

5 A sample of 3-(5-methyl-2-phenyl-oxazol-4-yl)-propionic acid (2.27 g, 9.82 mmol) was dissolved in anhydrous CH2Cl2 (20 mL) followed by addition of a catalytic amount of DMF (0.72 mL) and slow addition of a 2 M solution of oxalyl chloride (7.36 mL). The reaction mixture was stirred at room temperature for 24 h under N_2 . The solvent was removed 10 in vacuo to provide crude acid chloride which was then dissolved in 10 mL anhydrous CH2Cl2 and then added to a flask containing 2-methyl-2-phenoxy-3-thiophen-2-yl-propionic acid methyl ester (527167) (2.51 g, 9.11 mmol) in anhydrous CH₂Cl₂ (10 mL) at 0 °C under N₂. Anhydrous 1.0 M SnCl₄ 15 solution (5.6 mL) was then added dropwise at 0 °C. After 1 h, the reaction was checked by HPLC, it appeared that little product had formed. Another 3.3 mL of SnCl4 solution was added and allowed to stir for 24 h at room temperature. 20 When the starting materials were consumed, the reaction was quenched by adding 6 M HCl dropwise at 0 °C until solid forms (20 mL) and the aqueous phase was extracted with

PCT/US01/22616

CH₂Cl₂ (2 x 50 mL). The organic layer was washed with water (50 mL) and solvent removed to give an oil. Following column chromatography (gradient 5 % to 20 % EtOAc in hexane), 1.31 g (30%) of product was obtained: ¹H NMR (400 MHz, CDCl₃) & 7.95 (d, 2 H), 7.56 (d, 1 H), 7.38 (m, 3 H), 7.20 (m, 2 H), 6.84 (t, 1 H), 6.81 (m, 3 H), 3.72 (s, 3 H), 3.50 (d, 1 H), 3.33 (d, 1 H), 3.28 (t, 2 H), 2.89 (t, 2 H), 2.33 (s, 3 H), 1.41 (s, 3 H); MS (EI) 490.2 (M+H)⁺.

10 ... Step G

2-Methyl-3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propionyl]thiophen-2-yl}-2-phenoxy-propionic acid (515337)

Hydrolysis, using the procedure of Example 1, Step E,

provided 275 mg (94 %) of product from 300 mg of 2-methyl-3{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propionyl]-thiophen-2yl}-2-phenoxy-propionic acid methyl ester: ¹H NMR (400 MHz,
CDCl₃) δ 8.05 (d, 2 H), 7.60 (d, 1 H), 7.42 (m, 3 H), 7.20
(m, 2 H), 6.84 (t, 1 H), 6.81 (m, 3 H), 3.50 (d, 1 H), 3.35

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(t, 2 H), 3.33 (d, 1 H), 2.95 (t, 2 H), 2.40 (s, 3 H), 1.41 (s, 3 H); MS (EI) 476.0 (M+H)^{+} .

Example 91

5 <u>2-Methyl-3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-</u> thiophen-2-yl}-2-phenoxy-propionic acid

Step A

3-{5-[1-Hydroxy-3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]thiophen-2-yl}-2-methyl-2-phenoxy-propionic acid methyl
ester

A sample of 2-methyl-3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propionyl]-thiophen-2-yl}-2-phenoxy-propionic acid

15 methyl ester (1.00 g, 2.04 mmol) was dissolved in THF (40 mL) and MeOH (20 mL) and cooled to 0 °C. Sodium borohydride

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(115 mg, 3.06 mmol) was added and allowed to stir at 0 °C for 45 min. The reaction was monitored by HPLC. Upon the completion of the reaction, the bulk of the solvent was removed in vacuo and water (40 mL) was added. The mixture was acidified with 6 N HCl (20 mL) and stirred for 30 min. This aqueous mixture was then extracted with CH_2Cl_2 (2 x 50 mL). The organic fractions were combined, dried over NaCl, and solvent removed in vacuo to give a crude oil. Flash chromatography (gradient 20 % to 40 % EtOAc in hexane) provided 650 mg (65 %) of desired product: 1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 2 H), 7.47 (m, 3 H), 7.19 (m, 2 H), 6.96 (t, 1 H), 6.79 (m, 3 H), 6.68 (d, 2 H), 4.96 (m, 1 H), 3.72 (s, 3 H), 3.43 (d, 1 H), 3.29 (d, 1 H), 2.71 (m, 2 H), 2.30 (s, 3 H), 2.17 (m, 2 H), 1.42 (s, 3 H); MS (EI) 492.2 (M+H) $^+$.

Step B

2-Methyl-3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]thiophen-2-yl}-2-phenoxy-propionic acid methyl ester

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To a solution of triethylsilane (0.62 mL, 3.89 mmol) in CH_2Cl_2 (4 mL) at -20 °C, boron trifluoride diethyl etherate (0.49 mL, 3.89 mmol) was added. A solution of 3-{5-[1-

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hydroxy-3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-thiophen-2-y1}-2-methy1-2-phenoxy-propionic acid methyl ester (650 mg, 1.30 mmol) in CH₂Cl₂ (4 mL) was then added dropwise to the BF3 solution over 1 h, keeping the temperature at -15 °C. The reaction was stirred at 0 °C for 2 h. The reaction was quenched with 1 N NaOH (approx. 3.6 mL) diluted with 1.8 mL of water and the pH was adjusted to pH 4.0 using 1 N HCl and 1 N NaOH. The organic layer was separated and the aqueous layer was further extracted with CH2Cl2 (2 x 30 10 mL). The combined organic layers were then washed with 0.1 N HCl (30 mL) and water (2 x 30 mL). Xylene (15 mL) and NaCl were added and the organics were concentrated to dryness to yield a yellow oil. The product was used in the next step without further purification: 1H NMR (400 MHz, 15 CDCl₃) δ 7.95 (d, 2 H), 7.37 (m, 4 H), 7.20 (m, 1 H), 6.96 (t, 1 H), 6.84 (d, 2 H), 6.60 (dd, 2 H), 3.72 (s, 3 H), 3.41 (d, 1 H), 3.30 (d, 1 H), 2.78 (t, 2 H), 2.50 (t, 2 H), 2.24 (s, 3 H), 2.00 (m, 2 H), 1.43 (s, 3 H); MS (EI) 476.2

20

 $(M+H)^+$.

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Step C

2-Methyl-3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]thiophen-2-yl}-2-phenoxy-propionic acid

5 $2-Methyl-3-{5-[3-(5-methyl-2-phenyl-oxazol-4-yl)-}$ propyl]-thiophen-2-yl}-2-phenoxy-propionic acid methyl ester 400 mg) was dissolved in EtOH (10 mL), and then 5 N NaOH (3 mL) was added. This mixture was allowed to stir at 60 °C The mixture was cooled to room temperature and 10 then acidified to pH=2 by the dropwise addition of 5 N HCl. This acidic mixture was diluted with H2O (10 mL) and then extracted with CH2Cl2 (2 x 25 mL). The organic layers were combined, dried over NaCl, and solvent removed in vacuo which provided 354 mg (92 %) of desired acid: ¹H NMR (400 15 MHz, CDCl₃) δ 8.05 (d, 2 H), 7.39 (m, 4 H), 7.23 (m, 1 H), 7.03 (t, 1 H), 6.95 (d, 2 H), 6.70 (d, 1 H), 6.62 (d, 1 H), 3.40 (d, 1 H), 3.30 (d, 1 H), 2.80 (t, 2 H), 2.52 (t, 2 H), 2.27 (s, 3 H), 2.02 (m, 2 H), 1.44 (s, 3 H); MS (EI) 462.2 $(M+H)^+$.

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Example 92

2-(2-Methoxy-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared using the

representative Standard Procedure (E) from 3-(4-Hydroxyphenyl)-2-(2-methoxy-phenoxy)-2-methyl-propionic acid ethyl
ester and toluene-4-sulfonic acid 2-(5-methyl-2-phenyloxazol-4-yl)-ethyl ester. ¹H NMR (400MHz, CDCl₃): • 7.997.97 (m, 2H), 7.47 (dd, 3H, J = 5.08 Hz, 1.96 Hz), 7.18 (d,

2H, J = 8.60), 7.07 (td, 1H, J = 6.65 Hz, 1.56 Hz), 6.896.80 (m, 4H), 6.63 (dd, 1H, J = 7.82 Hz, 1.56 Hz), 4.21 (t,
2H, J = 6.26 Hz), 3.82 (s, 3H), 3.30 (d, 1H, J = 14.1 Hz),
3.10-3.04 (m, 3H), 2.41 (s, 3H), 1.30 (s, 3H). MS [ES+] m/z
exact mass calcd for C₂₉H₃₀NO₆ 488.2073, found 488.2086.

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Example 93

2-(2-Methoxy-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid

The title compound was prepared using the representative Standard Procedure (E) from 3-(4-Hydroxy-

5 representative Standard Procedure (E) from 3-(4-Hydroxy-pheny1)-2-(2-methoxy-phenoxy)-2-methy1-propionic acid ethy1 ester and toluene-4-sulfonic acid 2-(5-methy1-2-thiophen-2-y1-oxazo1-4-y1)-ethy1 ester. ¹H NMR (400MHz, CDCl₃): • 7.72 (d, 1H, J = 3.52 Hz), 7.45 (d, 1H, J = 3.52 Hz), 7.18 (d, 2H, J = 8.60 Hz), 7.12-7.05 (m, 2H), 6.88 (d, 1H, J = 7.82 Hz), 6.84-6.79 (m, 3H), 6.62 (d, 1H, J = 6.65 Hz), 4.19 (t, 2H, J = 6.26 Hz), 3.82 (s, 3H), 3.30 (d, 1H, J = 14.08 Hz), 3.08 (d, 1H, J = 14.08 Hz), 3.00 (t, 2H, J = 6.26 Hz), 2.37 (s, 3H), 1.30 (s, 3H). MS [ES+] m/z exact mass calcd for C₂₇H₂₈NO₆S 494.1637, found 494.1640.

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Example 94

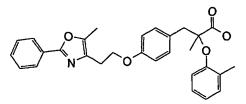
3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methoxy-phenoxy)-2-methyl-propionic acid

5 The title compound was prepared using the representative Standard Procedure (E) from 3-(4-Hydroxypheny1)-2-(2-methoxy-phenoxy)-2-methyl-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyloxazol-4-yl)-ethyl ester. ¹H NMR (400MHz, CDCl₃): δ 7.18(d, 2H, J = 8.21 Hz), 7.06 (t, 1H, J = 7.82 Hz), 6.88 (d, 1H, J10 = 8.21 Hz, 6.83-6.79 (m, 3H), 6.62 (d, 1H, J = 7.82 Hz), 4.12 (t, 2H, J = 6.65 Hz), 3.82 (s, 3H), 3.29 (d, 1H, J =14.08 Hz), 3.09 (d, 1H, J = 14.08 Hz). 2.85 (t, 2H, J = 6.65Hz), 2.70-2.63 (m, 1H), 2.21 (s, 3H), 1.99 (d, 2H, J = 12.51Hz), 1.77 (d, 2H, J = 12.90 Hz), 1.67 (d, 1H, J = 11.73 Hz, 15 1.50 (q, 2H, J = 12.51 Hz), 1.37-1.21 (m, 5H). MS [ES+] m/zexact mass calcd for C29H36NO6 494.2543, found 494.2562.

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Example 95

2-Methy1-3-{4-[2-(5-methy1-2-pheny1-oxazol-4-y1)-ethoxy]-phenyl}-2-o-tolyloxy-propionic acid

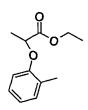


Step A

2-o-Tolyloxy-propionic acid ethyl ester

5

hexanes.



Cesium carbonate (53.86g, 165.3mmol) was added to a solution of 2-cresol (10.0g, 92.5mmol) in anhydrous DMF (500mL) at room temperature under an atmosphere of nitrogen. After five minutes, ethyl 2-bromopropionate (16.7mL, 10 92.5mmol, d=1.394) was added rapidly dropwise and the resultant mixture was allowed to stir at 90°C for 18h. The reaction mixture was diluted with diethyl ether, then extracted twice with 1N HCl and twice with water. The organic layer was dried over MgSO4 and concentrated in vacuo 15 to provide the title compound (19.7g, 100%). ¹H NMR $(400MHz, CDCl_3): \delta 7.16(d, 1H, J = 7.43 Hz), 7.11(t, 1H, J)$ = 7.43 Hz), 6.89 (t, 1H, J = <math>7.48 Hz), 6.70 (d, 1H, J = <math>7.43 Hz) Hz), 4.75 (q, 1H, J = 6.65 Hz), 4.23 (q, 2H, J = 6.65 Hz), 2.30 (s, 3H), 1.64 (dd, 3H, J = 7.04 Hz, 0.78 Hz,), 1.2620 (td, 3H, J = 7.04 Hz, 0.78 Hz). $R_f=0.37$ in 25% ether in

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Step B

3-(4-Benzyloxy-phenyl)-3-hydroxy-2-methyl-2-o-tolyloxy-propionic acid ethyl ester

A solution of LDA (34.9mL, 52.4mmol, 1.5M in 5 cyclohexane) in anhydrous THF (60mL) was cooled to -78°C in a dry ice/acetone bath and added to a solution of 2-o-Tolyloxy-propionic acid ethyl ester in anhydrous THF (60mL) also cooled to -78°C under an atmosphere of nitrogen. After five minutes, 4-benzyloxybenzaldehyde (5.56g, 26.2mmol) was added in one portion. After stirring for one minute, the reaction mixture was quenched with acetic acid (5mL, 87.4mmol, d=1.049) and a saturated solution of aqueous NH4Cl (50mL). The biphasic mixture was allowed to warm to room temperature and diluted with diethyl ether (1L). The organic layer was washed with water, dried over MgSO4, and 15 concentrated in vacuo. The residue was purified by flash column chromatography (13% ethyl acetate in hexanes) to provide a mixture of diastereomers of the titled compound (6.36g, 54%). ¹H NMR $(400MHz, CDCl_3)$: • 7.44-7.32 (m, 6H), 7.16-6.82 (m, 5H), 69.74-6.66 (m, 2H), 5.16 (d, 1H, J = 3.5220 Hz), 5.07 (s, 2H), 4.26-4.15 (m, 2H), 2.28 (s, 3H), 1.43 (s, 3H), 1.22-1.17 (m, 3H). $R_f=0.25$ in 25% ethyl acetate in hexanes.

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Step C

3-(4-Benzyloxy-phenyl)-3-hydroxy-2-methyl-2-o-tolyloxy-propionic acid ethyl ester

5 3-(4-Benzyloxy-phenyl)-3-hydroxy-2-methyl-2-o-tolyloxypropionic acid ethyl ester (6.36g, 15.7mmol) in anhydrous CH₂Cl₂ (140mL) was cooled to 0°C and treated with pyridine (13mL, 157.2mmol, d=0.987). Trifluoroacetic anhydride (6.7mL, 47.2mmol, d=1.487) was added dropwise and the 10 mixture was stirred for 2h, gradually warming to ambient temperature. The reaction mixture was diluted with diethyl ether and washed with 1N HCl, then water. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to produce the titled compound (7.4g, 91%) which was used without 15 purification. ¹H NMR (400MHz, CDCl₃): δ 7.43-7.31 (m, 7H), 7.11 (d, 1H, J = 7.43 Hz), 7.03-6.98 (m, 3H), 6.91 (t, 1H, J= 7.43), 6.69 (d, 1H, J = 8.21 Hz), 6.34 (s, 1H), 5.08 (s, 2H), 4.28-4.16 (m, 2H), 2.12 (s, 3H), 1.50 (s, 3H), 1.21 (td, 3H, J = 7.04 Hz, 0.78 Hz). $R_f=0.55$ in 25% ethyl acetate 20 in hexanes.

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Step D

3-(4-Hydroxy-phenyl)-2-methyl-2-o-tolyloxy-propionic acid ethyl ester

5 3-(4-Benzyloxy-phenyl)-2-methyl-2-o-tolyloxy-3-(2,2,2trifluoro-acetoxy)-propionic acid ethyl ester (7.4g, 14.3mmol) was dissolved in ethyl acetate (300mL), treated with 5% palladium on carbon (7.4g), and stirred under an atmosphere of hydrogen for 96 h. The suspension was 10 filtered through celite and concentrated in vacuo to provide the titled compound (4.8g, 100%) as an opaque yellow oil. ¹H NMR (400MHz, CDCl₃): • 7.14(d, 1H, J = 7.82 Hz), 7.07 t, 1H, J = 8.60 Hz), 7.01 (t, 1H, J = 7.82 Hz), 6.84 (t, 1H, J= 7.82 Hz), 6.72 (d, 2H, J = 8.60 Hz), 6.60 (d, 1H, J = 7.82Hz), 5.96 (s, 1H), 4.19-4.15 (m, 2H), 3.26 (d, 1H, J = 13.6915 Hz), 3.12 (d, 1H, J = 13.69), 2.17 (s, 3H), 1.44 (s, 3H), 1.18 (t, 3H, J = 7.04 Hz). . MS [ES+] m/z exact mass calcd for $C_{19}H_{26}NO_4$ 332.1862, found 332.1860.

20

Step E

3-{4-[2-(2-Biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methoxy-phenoxy)-2-methyl-propionic acid

PCT/US01/22616

Potassium carbonate (0.078g, 0.56mmol) was added to a solution of 3-(4-Hydroxy-phenyl)-2-methyl-2-o-tolyloxypropionic acid ethyl ester and toluene-4-sulfonic acid 2-(2biphenyl-4-yl-5-methyl-oxazol-4-yl)-ethyl ester in 4A sievedried ethanol (2mL). The resultant mixture was stirred at 80°C under an atmosphere of nitrogen for 18 h, then diluted with ethanol (2mL). 5N NaOH (0.5mL) was added, then the reaction mixture was refluxed for 2 h. The reaction mixture was concentrated in vacuo, diluted with 1N HCl, and extracted with CH2Cl2. The organic layer was dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS. ¹H NMR (400MHz, CDCl₃): • 7.96-7.92 (m, 2H), 7.40 (t, 3H, J = 3.13 Hz), 7.12 (d, 2H, J = 6.65 Hz), 7.06 (t, 1H, J = 7.82 Hz), 6.91 (t, 1H, J = 7.82 Hz), 6.80(t, 4H, J = 6.65 Hz), 4.17 (t, 2H, J = 6.65 Hz), 3.25 (d,1H, J = 14.08 Hz), 3.19 (d, 1H, J = 14.08 Hz), 2.98 (t, 2H, J = 6.65 Hz), 2.17 (s, 3H), 1.48 (s, 3H), 1.24 (s, 3H). MS [ES+] m/z exact mass calcd for $C_{29}H_{30}NO_5$ 472.2124, found 472.2129.

20

10

15

Example 96

2-Methy1-3-{4-[2-(5-methy1-2-thiophen-2-y1-oxazo1-4-y1)-ethoxy]-pheny1}-2-o-tolyloxy-propionic acid

25 The title compound was prepared using the representative Standard Procedure (E) from 3-(4-Hydroxy-phenyl)-2-methyl-2-o-tolyloxy-propionic acid ethyl ester and

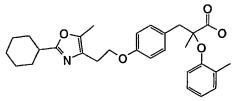
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toluene-4-sulfonic acid 2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethyl ester. 1 H NMR (400MHz, CDCl₃): • 7.59(dd, 1H, J = 3.91 Hz, 1.17 Hz), 7.36 (dd, 1H, J = 3.91 Hz, 1.17 Hz), 7.14-7.11 (m, 3H), 7.08-7.04 (m, 2H), 6.91 (t, 1H, J = 7.43 Hz), 6.82-6.77 (m, 3H), 4.15 (t, 2H, J = 6.65 Hz), 3.25 (d, 1H, J = 14.08 Hz), 3.19 (d, 1H, J = 14.08 Hz), 2.94 (t, 2H, J = 6.65 Hz), 2.33 (s, 3H), 2.17 (s, 3H, 1.48 (s, 3H). MS [ES+] m/z exact mass calcd for $C_{27}H_{28}NO_{5}S$ 478.1688, found 478.1676.

10

Example 97

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-o-tolyloxy-propionic acid



15 The title compound was prepared using the representative Standard Procedure (E) from 3-(4-Hydroxypheny1)-2-methy1-2-o-tolyloxy-propionic acid ethyl ester and toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4yl)-ethyl ester. ¹H NMR (400MHz, CDCl₃): δ 7.14-7.11 (m, 20 3H), 7.06 (t, 1H, J = 7.82 Hz), 6.91 (t, 1H, J = 7.82 Hz), 6.79 (d, 1H, J = 8.60 Hz), 6.75 (d, 2H, J = 8.60 Hz), 4.11 (t, 2H, J = 6.26 Hz), 3.24 (d, 1H, J = 14.08 Hz), 3.18 (d, 2H, 2H, 3Hz)1H, J = 14.08 Hz), 2.95 (t, 2H, J = 6.26 Hz), 2.90-2.87 (m, 1H), 2.29 (s, 3H), 2.17 (s, 3H), 2.02-1.99 (m, 2H), 1.81-25 1.78 (m, 2H), 1.71-1.68 (m, 1H), 1.58-1.52 (m, 2H), 1.47 (s, 3H), 1.38-1.21 (m, 5H). MS [ES+] m/z exact mass calcd for $C_{29}H_{36}NO_5$ 478.2593, found 478.2611.

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Example 98

2-Methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-2-o-tolyloxy-propionic acid

The title compound was prepared using the

representative Standard Procedure (E) from 3-(4-Hydroxyphenyl)-2-methyl-2-o-tolyloxy-propionic acid ethyl ester and
Toluene-4-sulfonic acid 2-[5-methyl-2-(1-methyl-cyclohexyl)oxazol-4-yl]-ethyl ester. ¹H NMR (400MHz, CDCl₃): δ 7.14-7.11
(m, 3H), 7.08-7.04 (m, 1H), 6.91 (t, 1H, J = 7.82 Hz), 6.81

(d, 1H, J = 8.60 Hz), 6.76 (d, 2H, J = 8.60 Hz), 4.10 (t,
2H, J = 6.26 Hz), 3.24 (d, 1H, J = 14.08 Hz), 3.18 (d, 1H, J
= 14.08 Hz), 2.93 (t, 2H, J = 6.26 Hz), 2.27 (s, 3H), 2.17
(s, 3H), 2.13-2.06 (m, 2H), 1.54-1.48 (m, 8H), 1.40-1.34 (m,
3H), 1.27 (s, 3H). MS [EI+] 492 (M+H)⁺, [EI-] 490 (M-H)⁺.

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Example 99

2-(3-Bromo-phenoxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid

Step A

5

2-(3-Bromo-phenoxy)-propionic acid ethyl ester

o O Br

Cesium carbonate (57.8g, 177.4mmol) was added to a solution of 3-bromophenol (10.23g, 59.1mmol) in anhydrous 10 DMF (500mL) at room temperature under an atmosphere of nitrogen. After five minutes, ethyl 2-bromopropionate (7.7mL, 59.1mmol, d=1.394) was added rapidly dropwise and the resultant mixture was allowed to stir at 90°C for 18h. The reaction mixture was diluted with diethyl ether and 15 extracted twice with 1N HCl and three times with water. The organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was purified by flash chromatography (25% ether in hexanes) to provide the titled compound (14.8g, 97%) as a light yellow oil. 1 H NMR (400MHz, CDCl₃): 20 δ 7.13-7.07 (m,3H), 7.02-7.13 (m, 1H), 6.79 (dt, 1H, J = 7.63 Hz, 2.35 Hz), 4.70 (q, 1H, J = 6.75 Hz), 4.23 (q, 2H, J

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= 3.52 Hz), 1.60 (d, 3H, J = 7.04 Hz), 1.24 (t, 3H, J = 7.04 Hz). R_f =0.36 in 25% ether in hexanes.

Step B

5 <u>3-(4-Benzyloxy-phenyl)-2-(3-bromo-phenoxy)-3-hydroxy-2-</u> methyl-propionic acid ethyl ester

A solution of LDA (39.7mL, 59.5mmol, 1.5M in cyclohexane) in anhydrous THF (90mL) was cooled to -78°C in 10 a dry ice/acetone bath and added to a solution of 2-(3-Bromo-phenoxy)-propionic acid ethyl ester in anhydrous THF (90mL) also cooled to -78°C under an atmosphere of nitrogen. After five minutes, 4-benzyloxybenzaldehyde (6.3g, 29.8mmol) was added in one portion. After stirring for one minute, 15 the reaction mixture was quenched with acetic acid (5.7mL, 99.2mmol, d=1.049) and a saturated solution of aqueous NH4Cl (80mL). The biphasic mixture was allowed to warm to room temperature and diluted with diethyl ether (1L). organic layer was washed with water, dried over MgSO4, and 20 concentrated in vacuo. The residue was purified by flash column chromatography (17% ethyl acetate in hexanes) to provide a mixture of diastereomers of 3-(4-Benzyloxypheny1)-2-(3-bromo-phenoxy)-3-hydroxy-2-methyl-propionic acid ethyl ester (10.0g, 62%). ¹H NMR (400MHz, CDCl₃): • 7.42-7.28 (m, 6H), 7.19-7.00 (m, 3H), 6.95 (dd, 2H, J = 6.7525 Hz, 1.76 Hz), 6.73 (dd, 1H, J = 6.45 Hz, 1.47 Hz), 5.21-5.02 (m, 3H), 4.24-4.14 (m, 2H), 4.08 (q, 2H, J=7.04 Hz), 3.39 (s, 1H), 1.23 (t, 3H, J=7.04 Hz). $R_f=0.22$ in 25% ethyl acetate in hexanes.

Step C

5

3-(4-Benzyloxy-phenyl)-2-(3-bromo-phenoxy)-2-methylpropionic acid ethyl ester

3-(4-Benzyloxy-phenyl)-2-(3-bromo-phenoxy)-3-hydroxy-2methyl-propionic acid ethyl ester (10.0g, 20.7mmol) was added slowly to a -20°C solution of triethylsilane (9.9mL, 10 62.0mmol, d=0.728) and boron trifluoride etherate (15.3mL, 124.0mmol, d=1.154) in anhydrous CH_2Cl_2 (370mL). The mixture was stirred for 6h, gradually warming to 0°C. The reaction mixture was quenched with a saturated solution of aqueous sodium carbonate and extracted with CH2Cl2. The 15 organic layer was dried over Na2SO4, concentrated in vacuo, and purified by flash column chromatography to provide the titled compound (3.7g, 38%). ¹H NMR (400MHz, CDCl₃): δ 7.46-7.33 (m, 5H), 7.18 (d, 2H, J = 8.60 Hz), 7.15-7.05 (m, 3H), 6.94 (dt, 2H, J = 8.60 Hz), 6.78 (dt, 1H, J = 7.82 Hz, 2.35 Hz), 4.23 (q, 2H, J = 7.04 Hz), 3.28 (d, 1H, J = 13.69 Hz), 3.19 (d, 1H, J = 13.69 Hz), 1.45 (s, 3H), 1.23 (t, 3H, J =7.04 Hz). $R_f=0.46$ in 25% ethyl acetate in hexanes.

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Step D

2-(3-Bromo-phenoxy)-3-(4-hydroxy-phenyl)-2-methyl-propionic acid ethyl ester

3-(4-Benzyloxy-phenyl)-2-(3-bromo-phenoxy)-2-methyl-5 propionic acid ethyl ester (3.7g, 7.8mmol) was dissolved in ethanol (140mL), treated with 5% palladium on carbon (0.37g), and stirred under an atmosphere of hydrogen for 2 The suspension was filtered through celite and concentrated in vacuo. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to 10 provide a mixture of the title compound and 3-(4-Hydroxyphenyl)-2-methyl-2-phenoxy-propionic acid ethyl ester as a light yellow oil (2.8g, 94%). 1 H NMR (400MHz, CDCl₃): δ 7.24-6.94 (m, 4H), 6.836.80 (m, 1H), 6.75-6.71 (m, 3H), 5.12 (s, 1H), 4.19 (q, 2H, J = 7.04 Hz), 3.24 (d, 1H, J = 13.6915 Hz), 3.06 (d, 1H, J = 13.69 Hz), 1.40 (s, 3H), 1.26-1.17 (m, 3H). MS [EI-] 377 $(M-H)^{+}$. $R_{f}=0.24$ in 25% ethyl acetate in hexanes.

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Step E

2-(3-Bromo-phenoxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid ethyl ester

Cesium carbonate (2.98g, 9.2mmol) was added to a 5 solution of 2-(3-Bromo-phenoxy)-3-(4-hydroxy-phenyl)-2methyl-propionic acid ethyl ester , 3-(4-Hydroxy-phenyl)-2methy1-2-phenoxy-propionic acid ethyl ester, and toluene-4sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester in DMF (60mL). The resultant mixture was stirred at 65°C under an atmosphere of nitrogen for 18 h, then diluted 10 with diethyl ether. The organic layer was washed with 1N HCl and water, dried over MgSO4, concentrated in vacuo, and purified by flash column chromatography (9% acetone in hexanes) to provide an unseparated mixture of 2-(3-Bromo-15 phenoxy) $-3-\{4-\{2-(2-cyclohexyl-5-methyl-oxazol-4-yl)$ ethoxy]-phenyl}-2-methyl-propionic acid ethyl ester and 3- $\{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl\}-2$ methyl-2-phenoxy-propionic acid ethyl ester (3.3g, 80%). H NMR (400MHz, CDCl₃): δ 7.24-6.92 (m, 5H), 6.81-6.69 (m, 3H), 20 4.20-4.10 (m, 5H), 3.22 (d, 1H, J = 13.69 Hz), 3.10 (d, 1H, J = 13.69 Hz), 2.84 (t, 2H, J = 6.65 Hz), 2.66 (tt, 1H, J =11.73 Hz, 3.52 Hz), 2.21 (s, 3H), 2.01 (d, 2H, J = 13.30Hz), 1.79-1.75 (m, 2H), 1.66 (d, 1H, J = 11.73 Hz), 1.55-1.17 (m, 6H). MS [EI+] 571 $(M+H)^{+}$.

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Step F

2-(3-Bromo-phenoxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic_acid

5 5N NaOH (0.5mL) was added to a solution of 2-(3-Bromophenoxy) $-3-\{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)$ ethoxy]-phenyl}-2-methyl-propionic acid ethyl ester and 3- $\{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl\}-2$ methyl-2-phenoxy-propionic acid ethyl ester in ethanol (4mL). The resultant mixture was refluxed under an 10 atmosphere of nitrogen for 2 h, then cooled to ambient temperature. The reaction mixture was concentrated in vacuo, diluted with 1N HCl, and extracted with CH2Cl2. organic layer was dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS. ¹H NMR 15 $(400MHz, CDCl_3): \delta 7.17 (m, 5H), 6.90-6.76 (m, 3H), 4.12 (t, 5H)$ 2H, J = 6.26 Hz), 3.22 (d, 1H, J = 13.69 Hz), 3.10 (d, 1H, J= 13.69 Hz), 2.95 (t, 2H, J = 6.26 Hz), 2.90-2.68 (m, 1H), 2.30 (s, 3H), 2.01 (d, 2H, J = 13.30 Hz), 1.79 (d, 2H, J =20 12.90 Hz), 1.69 (d, 1H, J = 13.30 Hz), 1.40 (s, 3H), 1.58-1.21 (m, 4H). MS [EI+] 543 $(M+H)^+$.

PCT/US01/22616 WO 02/16331

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Example 100

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-(3-thiophen-3-yl-phenoxy)-propionic acid

Step A

5

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 $3-\{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl\}-$ 2-methyl-2-(3-thiophen-3-yl-phenoxy)-propionic acid ethyl ester

Add palladium acetate (8mg, 0.04mmol) to a solution of 2-(3-Bromo-phenoxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4y1)-ethoxy]-pheny1}-2-methyl-propionic acid (0.204g, 0.36mmol), thiophene-3-boronic acid (91mg, 0.71mmol), triphenylphosphine (19mg, 0.07mmol), and potassium fluoride (51mg, 1.07mmol) in anhydrous THF (3mL). Reflux the 15 reaction mixture for 18 h under an atmosphere of nitrogen. Dilute the cooled reaction mixture with ethyl acetate and wash with water and brine. The organic layer was dried over Na₂SO₄, concentrated in vacuo, and purified by flash column chromatography (9% acetone in hexanes) to provide a mixture 20

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of the titled compound and 3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxy-propionic acid ethyl ester (70mg, 34%). ¹H NMR (400MHz, CDCl₃): δ 7.38-7.19 (m, 5H), 7.13(d, 2H, J = 8.60 Hz), 7.07 (m, 1H), 6.80 (2H, J = 8.60 Hz), 6.73-6.70 (m, 1H), 4.19(q, 2H, J = 7.04 Hz), 4.12 (t, 2H, J = 6.65 Hz), 3.27 (d, 1H, J = 13.69 Hz), 3.11 (d, 1H, J = 13.69 Hz), 2.85 (t, 2H, J = 6.65 Hz), 2.70-2.63 (m, 1H,), 2.22 (s, 3H), 2.01 (d, 2H, J = 11.73 Hz), 1.79-1.76 (m, 2H), 1.67 (h, 1H, J = 11.73 Hz), 1.59 (s, 3H), 1.56-1.46 (m, 2H), 1.41 (s, 3H), 1.37-1.23 (m, 2H), 1.20 (t, 3H, J = 7.04 Hz). MS [EI+] 574 (M+H)⁺. R_f=0.08 in 9% ethyl acetate in hexanes.

Step B

15 3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-(3-thiophen-3-yl-phenoxy)-propionic acid

5N NaOH (0.5mL) was added to a solution of 3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-(3-thiophen-3-yl-phenoxy)-propionic acid ethyl ester and 3-20 {4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxy-propionic acid ethyl ester in ethanol (4mL). The resultant mixture was refluxed under an atmosphere of nitrogen for 2 h, then cooled to ambient temperature. The reaction mixture was concentrated in vacuo, diluted with 1N HCl, and extracted with CH₂Cl₂. The organic layer was dried through a Varian ChemElut cartridge,

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concentrated in vacuo, and purified by LCMS. ¹H NMR (400MHz, CDCl₃): δ 7.39-7.26 (m, 5H), 7.17 (d, 2H, J = 8.60 Hz), 7.11-7.10 (m, 1H), 6.82-6.80 (m, 1H), 6.78 (d, 2H, J = 8.60 Hz), 4.11 (t, 2H, J = 6.26 Hz), 3.25 (d, 1H, J = 14.08 Hz), 3.13 (d, 1H, J = 14.08 Hz), 2.93 (t, 2H, J = 6.26 Hz), 2.87-2.81 (m, 1H), 2.28(s, 3H), 1.99 (d, 2H, J = 12.51 Hz), 1.77 (d, 2H, J = 12.51), 1.67 (d, 2H, J = 12.51), 1.57-1.46(m, 2H), 1.45 (s, 3H), 1.37-1.19 (m, 2H). MS [ES+] m/z exact mass calcd for $C_{32}H_{36}NO_{5}S$ 546.2314, found 546.2308.

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Example 101

2-(Biphenyl-3-yloxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid ethyl ester

Step A

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2-(Biphenyl-3-yloxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid ethyl ester

Add palladium acetate (8mg, 0.04mmol) to a solution of 2-(3-Bromo-phenoxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxyl-phenyl}-2-methyl-propionic acid (0.204g, 0.36mmol), thiophene-3-boronic acid (91mg, 0.71mmol), triphenylphosphine (19mg, 0.07mmol), and potassium fluoride (51mg, 1.07mmol) in anhydrous THF (3mL). Reflux the reaction mixture for 18 h under an atmosphere of nitrogen. Dilute the cooled reaction mixture with ethyl acetate and wash with water and brine. Dry the organic layer over Na₂SO₄, concentrate in vacuo, and purify by flash column chromatography (9% acetone in hexanes) to provide a mixture

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of the titled compound and $3-\{4-[2-(2-\text{Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl\}-2-methyl-2-phenoxy-propionic acid ethyl ester. ¹H NMR (400MHz, CDCl₃): <math>\delta$ 7.53 (d, 1H, J = 7.04 Hz), 7.41 (t, 1H, J = 7.82 Hz), 7.35-7.13 (m, 6H), 7.08-6.95 (m, 1H), 6.81 (s, 4H), 4.22-4.13 (m, 4H), 3.26 (d, 1H, J = 14.08 Hz), 3.14 (d, 1H, J = 14.08 Hz), 2.87-2.66 (m, 3H), 2.23 (s, 3H), 2.02 (d, 2H, J = 11.23 Hz), 1.80 (m, 10H), 1.21 (t, 3H, J = 7.04 Hz). MS [EI+] 568 (M+H)⁺. R_f =0.14 in 25% acetone in hexanes.

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Step B

2-(Biphenyl-3-yloxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid

5N NaOH (0.5mL) was added to a solution of 2-(Biphenyl-3-yloxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid ethyl ester and 3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxy-propionic acid ethyl ester in ethanol (4mL). The resultant mixture was refluxed under an atmosphere of nitrogen for 2 h, then cooled to ambient temperature. The reaction mixture was concentrated in vacuo, diluted with 1N HCl, and extracted with CH₂Cl₂. The organic layer was dried through a Varian ChemElut cartridge, concentrated in vacuo, and purified by LCMS. ¹H NMR

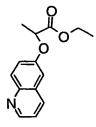
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= 7.04 Hz), 7.35-7.24 (m, 2H), 7.18 (d, 3H, J = 8.21 Hz), 7.12-7.11 (m, 1H), 6.86 (d, 1H, J = 8.60 Hz), 7.82 (d, 2H, J = 8.60 Hz), 4.13 (t, 2H, J = 5.47 Hz), 3.26 (d, 1H, J = 14.08 Hz), 3.14 (d, 1H, J = 14.08 Hz), 2.95 (t, 3H, J = 5.47 Hz), 2.29 (s, 3H), 2.00 (d, 2H, J = 12.51 Hz), 1.79 (d, 2H, J = 13.30 Hz), 1.70-1.21 (m, 8H). MS [EI+] 540 (M+H)⁺.

Example 104

2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]
phenyl}-2-(quinolin-6-yloxy)-propionic acid

Step A 2-(Quinolin-6-yloxy)-propionic acid ethyl ester



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A mixture of 2-bromo-propionic acid ethyl ester (14.6 mL, 0.112 mol), quinolin-6-ol (16.3 g, 0.112 mol) and Cs_2CO_3 (44 g, 0.135 mol) in 500 mL of DMF was heated to 90 °C for overnight. The mixture was filtered and diluted with Et_2O (500 mL). Organic layer was washed with water and brine. The combined aqueous layer was then extracted with EtOAC. Combined organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated. Crude material was purified by chromotography ($R_f = 0.3$ in hexanes/acetone = 1:1) to give 22 g of title compound as light yellow oil. 1H NMR (400 MHz, CDCl₃) $\delta\delta$ 8.78 (dd, 1H, J = 4.0, 0.8 Hz), 8.02 (d, 1H, J = 8.8 Hz), 8.01 (d, 1H, J = 4.0, 0.8 Hz), 8.02 (d, 1H, J = 8.8 Hz), 8.01 (d, 1H, J = 4.0, 0.8 Hz), 8.02 (d, 1H, J = 8.8 Hz), 8.01 (d, 1H, J = 4.0, 0.8 Hz), 8.02 (d, 1H, J = 8.8 Hz), 8.01 (d, 1H, J = 4.0)

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8.0Hz), 7.42 (dd, 1H, J = 9.4, 3.0 Hz), 7.35 (dd, 1H, J = 8.6, 4.2 Hz), 7.26 (d, 1H, J = 1.2 Hz), 6.99 (d, 1H, J = 2.8 Hz), 4.89 (q, 1H, J = 6.8 Hz), 4.27-4.20 (m, 2H), 1.69 (d, 3H, J = 6.8 Hz), 1.24 (t, 3H, J = 6.8 Hz).

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Step B

3-(4-Benzyloxy-phenyl)-2-methyl-2-(quinolin-6-yloxy)propionic acid ethyl ester

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To a LDA solution (42 mL, 1.5 M solution in THF) in 65 mL of dry THF at -78 °C, a solution of 2-(quinolin-6-yloxy)propionic acid ethyl ester (8.61 g, 0.035 mol) in 65 mL of dry THF was cannulated in. The resulting solution is allowed to stand at -78 °C for 3 min. Solid 4-benzyloxybenzaldehyde (6.71 g, 0.032 mol) was added and resulting mixture was allowed to stand at -78 °C for 5 min until all solid dissovled in the solution. Reaction was then quenched with AcOH (6.03 mL, 0.105 mol) in 60 mL of THF at -78 °C. The mixture was then diluted with Et₂O and washed with sat'NH4Cl , water and brine, dried over Na₂SO₄, filtered and concentrated. The crude material was purified by chromatography to give 3-(4-benzyloxy-phenyl)-3-hydroxy-2methyl-2-(quinolin-6-yloxy)-propionic acid ethyl ester in 86% yield. A of solution of 2.75 g of give 3-(4-benzyloxyphenyl)-3-hydroxy-2-methyl-2-(quinolin-6-yloxy)-propionic

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acid ethyl ester (6.01 mmol), trifluoroacetic acid (2.8 mL, 36.1 mmol), triethylsilane (5.8 mL, 36.1 mmol) in 80 mL of dichloroethane was heated to reflux for 50 h. The mixture was cooled to r.t. and diluted with Et₂O and washed with sat' NaHCO₃, water and brine. Organic layer was dried over Mg SO₄, filtered and concentrated. Residue was purified by chromatography (5% MeOH in CH₂Cl₂) to give 86% of title compound as light yellow oil. ¹H NMR (400 MHz, CDCl₃) $\delta\delta$ 8.78 (dd, 1H, J = 4.4, 1.6 Hz), 8.00 (d, 1H, J = 9.2 Hz), 7.98 (d, 1H, J = 8.8 Hz), 7.45-7.32 (m, 7H), 7.19 (d, 2H, J = 8.8 Hz), 7.04 (d, 1H, J = 3.2 Hz), 6.93 (d, 2H, J = 8.8 Hz), 5.06 (s, 2H), 4.23 (q, 2H, J = 7.1 Hz), 3.38, 3.18 (ABq, 2H, J = 13.8 Hz), 1.53 (s, 3H), 1.19 (t, 3H, J = 7.1 Hz). MS(ES⁺) m/z mass calcd for C₂₈H₂₈NO₄ (m + 1) 442, found 442.

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Step C

3-(4-Hydroxy-phenyl)-2-methyl-2-(quinolin-6-yloxy)-propionic acid ethyl ester

A solution of 3-(4-Benzyloxy-phenyl)-2-methyl-2
(quinolin-6-yloxy)-propionic acid ethyl ester
(2.65 g, 6.0 mmol) in 100 mL of EtOH with 5% Pd/C (530 mg,
20 w%) was allowed to stand under 1 atm H2 for 6 h.

Catalyst was filtered off and organic solvent was removed under vacuum. Residue was then dissolved in 200 mL of
toluene. 530 mg of 10% Pd/C was added. The mixture was heated to reflux under air for overnight. Reaction was

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cooled to r.t. and catalyst was filtered off. Organic solvent was removed under vacuum and crude material was clean for next step without further purification. 1H NMR (400 MHz, CDCl₃) $\delta\delta8.77$ (dd, 1H, J = 4.0, 1.4 Hz), 8.04 (d, 1H, J = 7.6 Hz), 8.02 (d, 1H, J = 9.6 Hz), 7.38 (dd, 1H, J =8.4, 4.4 Hz), 7.32 (dd, 1H, J = 9.2, 2.8 Hz), 7.09 (d, 2H, J= 8.8 Hz), 7.03 (d, 1H, J = 2.8 Hz), 6.83 (d, 2H, J = 8.8Hz), 4.22 (q, 2H, J = 7.1 Hz), 3.35, 3.13 (ABq, 2H, J = 13.6Hz), 1.52 (s, 3H), 1.19 (t, 3H, J = 7.1 Hz). $MS(ES^{\dagger}) m/z$ mass calcd for $C_{21}H_{22}NO_4$ (m + 1) 352, found 352. 10

Step D

$2-Methyl-3-\{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]$ phenyl}-2-(quinolin-6-yloxy)-propionic acid

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A solution of toluene-4-sulfonic acid 2-(5-methyl-2phenyl-oxazol-4-yl)-ethyl ester (94 mg, 0.26 mmol), 3-(4-Hydroxy-phenyl)-2-methyl-2-(quinolin-6-yloxy)-propionic acid ethyl ester (77.3 mg, 0.22 mmol) and K2CO3 (61 mg, 0.44 mmol) in 2 mL of EtOH was heated to 80 oC for overnight. Then 5N NaOH (0.26 mL, 1.3 mmol) was added and reaction mixture was stand at same temperature for 2 h. The mixture was cooled off to r.t. and organic solvent was removed under yacuum. Residue was then dissolved in CH2Cl2 and 1N HCl. Aqueous layer was washed with CH2Cl2 (2 x). Combined 25 organic layer was washed with brine, dried over Na2SO4,

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filtered and concentrated. Residue was purified by MS/LC to give title compound as white solid (55.6 mg, 50%). 1 H NMR (400 MHz, CDCl₃) $\delta\delta$ 8.76 (d, 1H, J = 4.4 Hz), 8.28 (d, 1H, J = 8.4 Hz), 7.94 (d, 1H, J = 9.2 Hz), 7.89-7.87 (m, 2H), 7.51-7.45 (m, 3H), 7.38-7.32 (m, 2H), 7.25-7.23 (m, 1H), 7.20 (d, 1H, J = 2.4 Hz), 7.16 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.17 (t, 2H, J = 6.6 Hz), 3.29, 3.11 (ABq, 2H, J = 13.4 Hz), 2.90 (t, 2H, J = 6.6 Hz), 2.33 (s, 3H), 1.42 (s, 3H). HRMS (ES⁺) m/z exact mass calcd for $C_{31}H_{29}N_2O_5$ (m+1) 509.2076, found 509.2095.

Example 105

3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}2-methyl-2-(quinolin-6-yloxy)-propionic

15 <u>acid</u>

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A solution of Toluene-4-sulfonic acid 2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethyl ester (96 mg, 0.26 mmol), 3-(4-Hydroxy-phenyl)-2-methyl-2-(quinolin-6-yloxy)-propionic acid ethyl ester (77.3 mg, 0.22 mmol) and K_2CO_3 (61 mg, 0.44 mmol) in 2 mL of EtOH was heated to 80 °C for overnight. Then 5N NaOH (0.26 mL, 1.3 mmol) was added and reaction mixture was stand at same temperature for 2 h. The mixture was cooled off to r.t. and organic solvent was removed under vacuum. Residue was then dissolved in CH_2Cl_2 and 1N HCl. Aqueous layer was washed with CH_2Cl_2 (2 x). Combined

organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated. Residue was purified by MS/LC to give title compound as white solid (54.5 mg, 48%). ¹H NMR (400 MHz, CDCl₃) $\delta\delta$ 8.74 (dd, 1H, J = 4.0, 1.6 Hz), 8.24 (d, 1H, J = 6.8 Hz), 7.92 (d, 1H, J = 9.2 Hz), 7.45 (dd, 1H, J = 8.2, 4.2 Hz), 7.33 (dd, 1H, J = 5.2, 2.8 Hz), 7.19 (d, 1H, J = 2.8 Hz), 7.15, 6.82 (ABq, 4H, J = 8.6 Hz), 4.08 (t, 2H, J = 6.8 Hz), 3.29, 3.11 (ABq, 2H, J = 13.8 Hz), 2.76 (t, 2H, J = 6.8 Hz), 2.68-2.63 (m, 1H), 2.18 (s, 3H), 1.93-1.87 (m, 2H),1.71-1.65 (m, 2H), 1.62-1.57 (m, 1H), 1.46-1.14 (m, 5H), 1.42 (s, 3H). HRMS (ES⁺) m/z exact mass calcd for $C_{31}H_{35}N_2O_5$ (m+1) 515.2546, found 515.2567.

Additional compounds of the present invention, having the structural formula shown below, were synthesized by methods similar to those described in the previous examples.

These additional compounds are further exemplified in the following table.

20 Table I

Example	R9	R6	R3	R7	meta R8	para R8
92	phenyl	Н	СНЗ	Н	Н	осн3
93	cyclohexyl	Н	СНЗ	Н	t-butyl	Н
94	phen-butyl	н	СНЗ	Н	Н	Н

_	2	1	6	_
_	~	_	v	

95	phenyl	осн3	СНЗ	Н	Н	H
96	morpholino	Н	сн3	H	Н	H
97	phenethyl	Н	СНЗ	H	H	H
98	phenethyl	Н	СНЗ	H	Н	t-butyl
99	phenethyl	H	СНЗ	H	H	F
100	phenethyl	н	СНЗ	H	осн3	н
101	phenethyl	н	СНЗ	H	СНЗ	Н
102	phenethyl	Н	СНЗ	H	CF3	н
103	phenethyl	H	СН3	H	Н	CF3
104	phenethyl	H	СНЗ	H	F	Н
105	phenethyl	Н	СНЗ	H	Н	Cl
106	phenethyl	Н	С2Н5	H	Н	H
107	phenethyl	Н	СН3	H	Н	OCF3
108	benzyl	н	СНЗ	H	Н	F
109	benzyl	Н	СНЗ	H	осн3	н
110	benzyl	н	СНЗ	Н	СНЗ	Н
111	benzyl	Н	СНЗ	H	CF3	Н
112	benzyl	Н	СНЗ	H	Н	CF3
113	benzyl	н	СНЗ	H	F	· H
114	benzyl	Н	СНЗ	Н	Н	C1
115	benzyl	н	С2Н5	Н	Н	H
116	benzyl	н	СНЗ	Н	H	OCF3
117	C ₂ H ₅	н	СН3	н	Н	Н
118	Br	Н	CH3	н	н	н
119	1-methyl- cyclohexyl	Н	CH3	Н	Н	CF3
120	3-thienyl	H	СН3	Н	Н	Н

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101		77	G113	OCTT2		Tr
121	phenyl	H	СН3	осн3	Н	H
122	2-thienyl	H	СНЗ	осн3	H	H
123	cyclohexyl	H	CH3	осн3	H ·	H
124	H ₃ C S	Н	CH3	н	н	СНЗ
125	phenyl	Н	СНЗ	СНЗ	H	Н
126	2-thienyl	H	CH3	СНЗ	Н	H .
127	cyclohexyl	Н	СН3	СНЗ	Н	Н
128	1-methyl- cyclohexyl	Н	СН3	СНЗ	Н	Н
129	t-butyl	Н	СНЗ	Н	H	H
130	H ₃ C S	H	СН3	H	Н	CF3
131	cyclohexyl	H	СН3	Н	H	t-butyl
132	morpholino	H	СН3	Н	H	t-butyl
133	cyclohexyl	н	СНЗ	Н	3- thienyl	Н
134	cyclohexyl	H	СНЗ	н	phenyl	H
135	cyclohexyl	Н	СН3	Н	Br	H
136	cyclohexyl	Н	СН3	Н	Н	t-butyl
137	phenyl	H	СНЗ	Н	Cl	H
138	2-thienyl	Н	СН3	Н	Cl	H
139	1-methyl- cyclohexyl	Н	СНЗ	Н	C1	H .
140	1-methyl- cyclohexyl	H	СН3	F	Ħ	н

Other compounds of the present invention, having the structural formula shown below, were also synthesized by methods similar to those described in the previous examples.

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These additional compounds are further exemplified in the following table.

Table II

Example	R9	R4		
141	phenyl	quinolyl		
142	2-thienyl	quinolyl		
143	cyclohexyl	quinolyl		
144	phenyl	1,2,3,4-tetrahydronaphthyl		
145	cyclohexyl	1,2,3,4-tetrahydronaphthyl		
146	1-methyl-cyclohexyl	1,2,3,4-tetrahydronaphthyl		
147	phenyl	pyridyl		

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Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPAR• and PPAR• receptors were determined by the procedures detailed below. DNA-dependent binding (ABCD binding) was carried out using SPA technology with PPAR receptors. Tritium-labeled PPAR α and PPAR γ agonists were used as radioligands for generating displacement curves and IC50

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values with compounds of the invention. Cotransfection assays were carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs and RXRa were constitutively expressed using plasmids containing the CMV promoter. For PPARa and PPARB, interference by endogenous PPARy in CV-1 cells was an issue. In order to eliminate such interference, a GAL4 chimeric system was used in which the DNA binding domain of the transfected PPAR was replaced by that of GAL4, and the GAL4 10 response element was utilized in place of the AOX PPRE. Cotransfection efficacy was determined relative to PPARa agonist and PPARy agonist reference molecules. Efficacies were determined by computer fit to a concentration-response 15 curve, or in some cases at a single high concentration of agonist (10 µM). For binding or cotransfection studies with receptors other than PPARs, similar assays were carried out using appropriate ligands, receptors, reporter constructs, etc., for that particular receptor.

These studies were carried out to evaluate the ability of compounds of the invention to bind to and/or activate various nuclear transcription factors, particularly huPPARa ("hu" indicates "human") and huPPARa. These studies provide in vitro data concerning efficacy and selectivity of compounds of the invention. Furthermore, binding and cotransfection data for compounds of the invention were compared with corresponding data for marketed compounds that act on either huPPARa or huPPARa.

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Binding and cotransfection data for representative compounds of the invention are compared with corresponding data for reference compounds in Table III.

Example	huPPARα		huPPARy	
	IC ₅₀ (nM)	CTF	IC ₅₀ (nM)	CTF
		Efficacy		Efficacy
		(웅)		(왕)
1	40	70	10	79
2	1250	59	476	400
3	22	70	7	74
4	39	80.	9	63
5	542	65	170	75
6	23	72	7	70
7	27	82	58	72
8	63	54	24	75
9	41	61	11	73
17	68	129	67	105
18	72	102	60	112
19	85	64	80	23
22	70	51	85 ·	12
23	63	40	81	17
25	73	95	70	106
27	75	46	76	15
29	116	65	48	82
31	53	63	19	73
34	91	112	77	76

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35 66 78 79 21 36 72 70 88 21 40 50 77 10 110 41 66 49 109 11 44 157 54 159 73 49 175 63 655 58 51 64 152 80 48 52 62 108 76 61 58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 <th></th> <th></th> <th></th> <th></th> <th></th>					
40 50 77 10 110 41 66 49 109 11 44 157 54 159 73 49 175 63 655 58 51 64 152 80 48 52 62 108 76 61 58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 <td>35</td> <td>66</td> <td>78</td> <td>79</td> <td>21</td>	35	66	78	79	21
41 66 49 109 11 44 157 54 159 73 49 175 63 655 58 51 64 152 80 48 52 62 108 76 61 58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 <	36	72	70	88	21
44 157 54 159 73 49 175 63 655 58 51 64 152 80 48 52 62 108 76 61 58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 Feno- 68,000	40	- 50	77	10	110
49 175 63 655 58 51 64 152 80 48 52 62 108 76 61 58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- tazone 94,500 0 1180 80 Feno- fibric 68,000 16 125,000 0	41	66	49	109	11
51 64 152 80 48 52 62 108 76 61 58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- tazone 94,500 0 1180 80 Feno- fibric 68,000 16 125,000 0	44	157	54	159	73
52 62 108 76 61 58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- tazone 94,500 0 1180 80 Feno- fibric 68,000 16 125,000 0	49	175	63	655	58
58 60 149 66 41 61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- tazone 94,500 0 1180 80 Feno- fibric 68,000 16 125,000 0	51 .	64	152	80	48
61 64 52 84 12 62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- tazone 94,500 0 1180 80 Feno- fibric 68,000 16 125,000 0	52	62	108	76	61
62 58 101 79 35 64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0	58	60	149	66	41
64 67 50 112 11 65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- tazone 94,500 0 1180 80 Feno- fibric 68,000 16 125,000 0	61	64	52	84	12
65 71 46 82 24 67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone 68,000 16 125,000 0 fibric 125,000 0 10 10	62	58	101	79	35
67 61 34 65 11 71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone 68,000 16 125,000 0 fibric 125,000 0 0	64	67	50	112	11
71 78 142 81 50 76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0 fibric 125,000 0	65	71	46	82	24
76 76 63 83 24 78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0 fibric 16 125,000 0 0	67	61	34	65	11
78 75 52 89 17 80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0	71	78	142	. 81	50
80 76 84 80 30 86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0 fibric 125,000 0	76	76	63	83	24
86 55 24 72 7 88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0 fibric 125,000 0	78	75	52	89	17
88 58 61 16 78 91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0	80	76	84	80	30
91 215 47 51 62 Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0 fibric	86	55	24	72	7
Trogli- 94,500 0 1180 80 tazone Feno- 68,000 16 125,000 0 fibric	88	58	61	16	78
tazone Feno- 68,000 16 125,000 0 fibric	91	215	47	51	62
Feno- 68,000 16 125,000 0 fibric	Trogli-	94,500	0	1180	80
fibric	tazone				
	Feno-	68,000	16	125,000	0
acid	fibric	1			
	acid				

*; >:

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Evaluation of Triglyceride and Cholesterol Level in HuapoAI Transgenic Mice

Five to six week old male mice, transgenic for human apoAI [C57Bl/6-tgn(apoal)1rub, Jackson Laboratory, Bar Harbor, ME] were housed five per cage (10"X20"X8" with aspen 5 chip bedding) with food (Purina 5001) and water available at all times. After an acclimation period of 2 weeks, animals were individually identified by ear notches, weighed, and assigned to groups based on body weight. Beginning the following morning, mice were dosed daily by oral gavage for 10 7 days using a 20 gauge, 14" curved disposable feeding needle (Popper & Sons). Treatments were test compounds (30 mg/kg), a positive control (fenofibrate, 100 mg/kg) or vehicle [1% carboxymethylcellulose (w/v) / 0.25% Tween80 (w/v); 0.2 ml/mouse]. Prior to termination on day 7, mice 15 were weighed and dosed. Three hours after dosing, animals were anesthetized by inhalation of isoflurane (2-4%; Abbott Laboratories, Chicago, IL) and blood obtained via cardiac puncture (0.7-1.0 ml). Whole blood was transferred to serum separator tubes (Vacutainer SST), chilled on ice, and 20 permitted to clot. Serum was obtained after centrifugation at 4°C and frozen until analysis for triglycerides, total cholesterol, compound levels, and serum lipoprotein profile by fast protein liquid chromatography (FPLC) coupled to an 25 inline detection system. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads were excised and weighed.

The animals dosed with vehicle had average triglycerides values of 60-80 mg/dl, which were reduced by the positive control fenofibrate (33-58 mg/dl with a mean reduction of 37%). The animals dosed with vehicle had

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average total serum cholesterol values of 140-180 mg/dl, which were increased by fenofibrate (190-280 mg/dl, with a mean elevation of 41%). Triglyceride serum levels for animals receiving compounds of the invention are reported in Table IV in mg/dl. When subject to FPLC analysis, pooled sera from vehicle-treated hu apoAI transgenic mice had a high density lipoprotein cholesterol (HDLc) peak area which ranged from 47 v-sec to 62 v-sec. Fenofibrate increased the amount of HDLc (68-96 v-sec with a mean percent increase of 48%). Test compounds are reported in terms of percent increase in the area under the curve as indicated in Table V.

Table IV: Triglyceride serum levels in mice receiving a compound of the invention.

Example	Reduction in
	Triglyceride
	Serum Level
	(Percent)
1	41.3
2	-12.9
4	58.3
5	19.7
6	38.5
7	42.1
9	19.8
17	78.7
18	69.0
19	40.0
22	19.5
23	52.5
25	35.5
27	36.8
34	57.1
35	32.3
36	23.0
40	77.6
41	57.8
51	72.8
52	75.9
58	26.5
61	17.6

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62	2.5
64	43.0
65	. 54.0
67	67.8
76	27.1
78	64.8
80	36.6
86	30.1

Table V

Percent increase of HDLc serum levels in mice receiving a

compound of the invention over mice receiving vehicle

Example	% HDLc Increase		
1	83		
2	25		
3	67		
4	24		
5	30		
6	85		
7	39		
8	34		
9	123		
17	119		
18	141		
19	89		
22	29		
23	54		
25	. 8		
27	49		
29	78		

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31	114
34	95
35	77
36	30
40	131
41	96
44	151
49	17
51	122
52	185
58	74
61	72
62	72
64	66
65	75
67	76
71	34
76	26
78	95
80	123
86	36
88	86
91	46

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Evaluation of Glucose Levels in db/db Mice

Five week old male diabetic (db/db) mice [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates (db+) were housed 6 per cage (10"X20"X8" with 5 aspen chip bedding) with food (Purina 5015) and water available at all times. After an acclimation period of 2 weeks, animals were individually identified by ear notches, weighed, and bled via the tail vein for determination of initial glucose levels. Blood was collected (100 µl) from 10 unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube (Fisher) balanced on the edge of the bench. Sample was discharged into a heparinized microtainer with gel separator (VWR) and 15 retained on ice. Plasma was obtained after centrifugation at 4°C and glucose measured immediately. Remaining plasma was frozen until the completion of the experiment, when glucose and triglycerides were assayed in all samples. Animals were grouped based on initial glucose levels and 20 body weights. Beginning the following morning, mice were dosed daily by oral gavage for 7 days using a 20 gauge, 11/2" curved disposable feeding needle. Treatments were test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v) / 0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice were weighed and bled. 25 (tail vein) 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals were bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 were assayed for glucose. After the 24 hour bleed, animals were weighed and dosed for the final time. Three 30 hours after dosing on day 8, animals were anesthetized by

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inhalation of isoflurane and blood obtained via cardiac puncture (0.5-0.7 ml). Whole blood was transferred to serum separator tubes, chilled on ice and permitted to clot. Serum was obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads were excised and weighed.

The animals dosed with vehicle had average triglycerides values of 170-230 mg/dl, which were reduced by the positive PPARy control (70-120 mg/dl with a mean reduction of 50%). Male db/db mice were hyperglycemic (average glucose of 680-730 mg/dl on the 7th day of treatment), while lean animals had average glucose levels between 190-230 mg/dl. Treatment with the positive control agent reduced glucose significantly (350-550 mg/dl with a mean decrease towards normalization of 56%). Test compounds are reported in Table VI in terms of glucose normalization (i.e., 100% normalization would be glucose levels in treated db/db mice which did not differ from lean values.

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Glucose was measured colorimetrically using commercially purchased reagents (Sigma #315-500). According to the manufacturers, the procedures were modified from published work (McGowan, M. W., Artiss, J. D., Strandbergh, D. R. & Zak, B. Clin Chem, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte, coupled with a color reaction first described by Trinder (Trinder, P. Determination of glucose in blood using glucose oxidase with an alternative oxygen 30 acceptor. Ann Clin Biochem, 6:24 (1969)). The absorbance of

the dye produced is linearly related to the analyte in the sample. The assays were further modified in our laboratory for use in a 96 well format. Standards (Sigma #339-11, Sigma #16-11, and Sigma #CC0534 for glucose, triglycerides and total cholesterol, respectively), quality control plasma (Sigma # A2034), and samples (2 or 5 μ l/well) were measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 μ l \cdot water, provided a blank for each specimen. Plates were 10 incubated at room temperature (18, 15, and 10 minutes for glucose, triglycerides and total cholesterol, respectively) on a plate shaker (DPC Micormix 5) and absorbance read at 500 nm (glucose and total cholesterol) or 540 nm (triglycerides) on a plate reader (Wallac Victor 1420). Sample absorbances were compared to a standard curve (100-15 800, 10-500, and 100-400 mg/dl for glucose, triglycerides and total cholesterol, respectively). Values for the quality control sample were always within the expected range and the coefficient of variation for samples was below 10%. 20 All samples from an experiment were assayed at the same time to minimize inter-assay variability.

Serum lipoproteins were separated and cholesterol quantitated with an in-line detection system. Sample was applied to a Superose® 6 HR 10/30 size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16 ml/min mixed with the column effluent through a T-connection and the mixture passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37 C water bath. The colored product produced in the presence of cholesterol was monitored in the flow

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stream at 505 nm and the analog voltage from the monitor was converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration was plotted vs time and the area under the curve corresponding to the elution of VLDL, LDL and HDL was calculated using Perkin Elmer Turbochrome software.

Table VI Percent glucose normalisation values in db/db mice.

Example	Glucose
	Normalisation
1	95
2	9
3	85
4	74
5	80
6	86
7	86
8	97
9	95
17	112
18	110
19	95
22	85
23	97
25	73
27	86
29	86
34	80
35	84

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36	92
40	103
41	101
44	83
51	88
52	98
58 .	81
61	79
62	79
64	97
65	99
67	96
71	97
76	97
78	86
80	83
86	92
88	92
. 91	71

EQUIVALENTS

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While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

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CLAIMS

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We claim:

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5 1. A compound represented by the following structural formula:

and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 an unsubstituted or substituted group selected from aryl, heteroaryl, cycloalkyl, heterocyclo-alkyl, aryl-C1-C4 alkyl, heteroaryl-C1-C4 alkyl, cycloalkyl-C1-C4 alkyl, or t-butyl;
- (b) R2 is H, C1-C4 alkyl, C1-C4 haloalkyl or phenyl;
- (c) n is 2, 3, or 4;
- (d) W is is CH_2 , CH(OH), C(O) or O;
- (e) Y is an unsubstituted or substituted group consisting of thiophen-2,5-diyl or phenylene;
- (f) R3 is a C1-C4 alkyl or C1-C4 haloalkyl;
- (g) R4 is a substituted or unsubstituted phenyl,

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(h) naphthyl, 1,2,3,4-tetrahydronaphthyl, pyridyl, quinolyl or benzo[1,3]dioxol-5-yl group; and

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- (i) R5 is H, C1-C4 alkyl, or aminoalkyl.
- 5 2. A compound of Claim 1 comprising 2-(2-Methoxy-phenoxy)-2-methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid.
- 3. A compound of Claim 1 comprising which is 2-(2-Methoxyphenoxy)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yloxazol-4-yl)-ethoxy]-phenyl}-propionic acid.
 - 4. A compound of Claim 1 comprising 3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-(2-methoxy-phenoxy)-2-methyl-propionic acid.
 - 5. A compound of Claim 1 comprising 2-Methyl-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-2-o-tolyloxy-propionic acid.

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- 6. A compound of Claim 1 comprising 2-Methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-o-tolyloxy-propionic acid.
- 7. A compound of Claim 1 comprising 2-Methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}-phenyl)-2-o-tolyloxy-propionic acid.
- 8. A compound of Claim 1 comprising 3-{4-[2-(2-Cyclohexyl-30 5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-o-tolyloxy-propionic acid.
 - 9. A compound of Claim 1 comprising 2-Methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)-oxazol-4-yl]-ethoxy}phenyl)-2-o-tolyloxy-propionic acid.

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10. A compound of Claim 1 comprising 3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-(3-thiophen-3-yl-phenoxy)-propionic acid.

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- 11. A compound of Claim 1 comprising 2-(Biphenyl-3-yloxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid ethyl ester.
- 10 12. A compound of Claim 1 comprising 2-(3-Chloro-phenoxy)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-propionic acid.
- 13. A compound of Claim 1 comprising 2-(3-Chloro-phenoxy)
 2-methyl-3-(4-{2-[5-methyl-2-(1-methyl-cyclohexyl)
 oxazol-4-yl]-ethoxy}-phenyl)-propionic acid
 - 14. A compound of Claim 1 wherein n is 2.
- 20 15. A compound of Claims 1 or 2 wherein W is O.
 - 16. A compound of Claims 1, 2 or 3 wherein Y is phenylene.
- 17. A compound of Claims 1, 2, 3 or 4 wherein R2 and R3 are each methyl.
 - 18. A compound of Claims 1, 2, 3, 4 or 5 wherein R4 is substituted or unsubstituted phenyl.
- 30 19. A compound of Claims 1, 2, 3, 4, 5, or 6 wherein R5 is H.
 - 20. A compound represented by the following structural formula:

and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

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R1 an unsubstituted or substituted group (a) selected from aryl, heteroaryl, cycloalkyl, heterocyclo-alkyl, aryl-C1-C4 alkyl, heteroaryl-C1-C4 alkyl, cycloalkyl-C1-C4 alkyl, or t-butyl;

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(b) R2 is H, C1-C4 alkyl, C1-C4 haloalkyl or phenyl;

(c) R5 is H, C1-C4 alkyl, or aminoalkyl;

(d) R6 are each, independently, H, C1-C4 alkyl or C1-C4 alkoxy;

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R7 are each, independently, H, halo, C1-C4 (e) alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl or phenyl;

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R8 are each, independently, H, halo, C1-C4 (f) alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl, phenyl or together with the phenyl to which they are bound form

naphthyl, 1,2,3,4-tetrahydronaphthyl,
quinolyl or benzo[1,3]dioxol-5-yl; and

- (g) R9 is C1-C4 alkyl or C1-C4 haloalkyl.
- 5 21. A compound of Claim 8 wherein R2 and R9 are each methyl.
 - 22. A compound of Claims 8 or 9 wherein each R6 is H.
- 10 23. A compound of Claims 8, 9, or 10 wherein R5 is H.
 - 24. The compound represented by the following structural formula:

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and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R5 is H, C1-C4 alkyl, or aminoalkyl;
 - (b) R6 are each, independently, H, C1-C4 alkyl or C1-C4 alkoxy;
 - (c) R7 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl or phenyl;

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(d) R8 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl, phenyl or together with the phenyl to which they are bound form naphthyl, 1,2,3,4-tetrahydronaphthyl, quinolyl or benzo[1,3]dioxol-5-yl; and

- (e) R10 is an unsubstituted or substituted group selected from phenyl, 2-thienyl, 3-thienyl, cyclohexyl or 1-methyl-cyclohexyl.
- 25. A compound of Claim 12 wherein R5 is H.

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26. A compound represented by the following structural formula:

and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R7 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl or phenyl; and
- (b) R8 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4

haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl, phenyl or together with the phenyl to which they are bound form naphthyl, 1,2,3,4-tetrahydronaphthyl, quinolyl or benzo[1,3]dioxol-5-yl.

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27. A compound of Claim 14 comprising 3-{4-[2-(2-Pheny1-5-methyl-oxazo1-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxy-propionic acid.

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- 28. A compound of Claim 15 comprising (S)-3-{4-[2-(2-Phenyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-phenoxy-propionic acid.
- 15 29. A compound represented by the following structural formula:

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and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

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(a) R7 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl or phenyl; 5

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- (b) R8 are each, independently, H, halo, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, nitro, methanesulfonyl, C3-C8 cycloalkyl, thienyl, phenyl or together with the phenyl to which they are bound form naphthyl, 1,2,3,4-tetrahydronaphthyl, quinolyl or benzo[1,3]dioxol-5-yl; and
- (c) R11 is H, C1-C4 alkyl or halo.
- 10 30. A compound of Claim 17 comprising 2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxy]-phenyl}-2-phenoxypropionic acid.
- 31. A compound of Claim 18 comprising (S)-2-Methyl-3-{4-[2-15] (5-methyl-2-thiophen-2-yl-oxazol-4-yl)-ethoxyl-phenyl}-2-phenoxypropionic acid.
 - 32. A compound of Claim 17 comprising 3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-p-tolyloxy-propionic acid.
 - 33. A compound of Claim 20 comprising (S)-3-{4-[2-(2-cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-p-tolyloxy-propionic acid.

34. A compound represented by the following structural formula:

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and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 an unsubstituted or substituted group selected from aryl, heteroaryl, cycloalkyl, heterocyclo-alkyl, aryl-C1-C4 alkyl, heteroaryl-C1-C4 alkyl, cycloalkyl-C1-C4 alkyl, or t-butyl;
 - (b) R2 is H, C1-C4 alkyl, C1-C4 haloalkyl or phenyl;
 - (c) V is is C, C(OH) or C(O);
 - (d) R3 is a C1-C4 alkyl or C1-C4 haloalkyl;
 - (e) R4 is a substituted or unsubstituted phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, quinolyl or benzo[1,3]dioxol-5-yl group; and
 - (f) R5 is H, C1-C4 alkyl, or aminoalkyl.
- 35. A compound of Claims 1-22 wherein said compound is radiolabeled.
- 36. A compound of Claims 1-22 wherein said compound is tritiated.
- 37. A compound which is 2-Methy1-3-{4-[2-(5-methy1-2-pheny1-oxazol-4-y1)-ethoxy]-pheny1}-2-(quinolin-6-yloxy)-propionic acid.
 - 38. A compound which is 3-{4-[2-(2-Cyclohexyl-5-methyl-oxazol-4-yl)-ethoxy]-phenyl}-2-methyl-2-(quinolin-6-yloxy)-propionic acid.

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39. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and at least one compound of Claims 1-22, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

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- 40. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound of Claims 1-22, or a pharmaceutically acceptable salt, solvate or hydrate thereof.
- 41. The method of Claim 26, wherein the peroxisome proliferator activated receptor is an α receptor.
- 15 42. The method of Claim 27, wherein the peroxisome proliferator activated receptor is an γ receptor.
- 43. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the 20 mammal a therapeutically effective amount of at least one compound of Claims 1-22, or a pharmaceutically acceptable salt, solvate or hydrate thereof.
- 44. A method of preventing diabetes mellitus in a mammal,

 comprising the step of administering to the mammal a

 effective amount of at least one compound of Claims 1
 22, or a pharmaceutically acceptable salt, solvate or

 hydrate thereof.
- 30 45. The method of Claim 29 or 30 wherein the mammal is a human.

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- 46. The method of Claim 31 wherein the compound potentiates a peroxisome proliferator activated receptor.
- 5 47. The method of Claim 32 wherein the peroxisome proliferator activated receptor is a γ receptor.
 - 48. The method of Claim 29 or 30 wherein the compound lowers blood glucose levels.

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- 49. A method of treating cardiovascular disease in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-22, or a pharmaceutically acceptable salt, solvate or hydrate thereof.
- 50. A method of preventing cardiovascular disease in a mammal, comprising the step of administering to the mammal an effective amount of at least one compound of Claims 1-22, or a pharmaceutically acceptable salt, solvate or hydrate thereof.
- 51. The method of Claim 35 or 36 wherein the mammal is a human.

- 52. The method of Claim 37, wherein the compound potentiates a peroxisome proliferator activated receptor.
- 30 53. The method of Claim 38 wherein the peroxisome proliferator activated receptor is an α receptor.

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- 54. The method of Claim 35 or 36 wherein the compound lowers triglycerides in the mammal.
- 5 55. The method of Claim 35 or 36 wherein the compound lowers low density lipoproteins in the mammal.
 - 56. The method of Claim 35 or 36 wherein the compound increases high density lipoproteins in a mammal.

- 57. A method of treating Syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-22, or a pharmaceutically
- 15 acceptable salt, solvate or hydrate thereof.
 - 58. A method of preventing Syndrome X in a mammal, comprising the step of administering to the mammal an effective amount of at least one compound of Claims 1-22, or a pharmaceutically acceptable salt, solvate or
- 20 22, or a pharmaceutically acceptable salt, solvate or hydrate thereof.
 - 59. The method of Claim 43 or 44 wherein the compound potentiates a peroxisome proliferator activated
- 25 receptor.
 - 60. The method of Claim 45 wherein the compound lowers blood glucose levels.
- 30 61. The method of Claim 43 or 44 wherein the compound lowers serum concentration of triglycerides in the mammal.

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62. The method of Claim 43 or 44 wherein the compound lowers serum concentration of low density lipoproteins in the mammal.

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- 63. The method of Claim 43 or 44 wherein the compound increases serum concentration of high density lipoproteins in a mammal.
- 10 64. A compound for use in therapy for a disorder modulated by a peroxisome proliferator activated receptor, wherein the compound, or pharmaceutically acceptable salt, solvate or hydrate thereof, is a compound of Claims 1-22.

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- 65. Use of a compound for the manufacture of a medicament for the treatment of a condition modulated by a peroxisome proliferator activated receptor, wherein the compound, or pharmaceutically acceptable salt, solvate or hydrate thereof, is a compound of Claims 1-22.
- 66. A compound of Claim 1 and named in any one of the Examples herein, or a physiologically acceptable salt, solvate or hydrate thereof.

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67. A process for the preparation of a compound of Claim 1, or a physiologically tolerable salt, solvate or hydrate thereof, substantially as described in any one of the Examples herein.

INTERNATIONAL SEARCH REPORT

Inte onal Application No PC 1/US 01/22616

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D263/32 C07D C07D413/12 C07D413/14 C07D413/06 CO7D413/04 A61K31/421 A61K31/422 A61K31/4439 A61K31/4709 A61P3/10 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) CO7D A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) BEILSTEIN Data, EPO-Internal, WPI Data, CHEM ABS Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Category ° Α SARGES R ET AL: "Glucose 1 transport-enhancing and hypoglycemic activity of 2-methyl-2-phenoxy-3phenylpropanoic acids" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 24, 22 November 1996 (1996-11-22), pages 4783-4803, XP002184224 the whole document Further documents are listed in the continuation of box C. Patent family members are listed in annex. X Special categories of cited documents: T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the *A* document defining the general state of the art which is not considered to be of particular relevance Invention *E* earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "O" document referring to an oral disclosure, use, exhibition or other means document published prior to the International filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the International search report 28 November 2001 11/12/2001 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 Allard, M

INTERNATIONAL SEARCH REPORT

Inta onal Application No PCI/US 01/22616

		PC1/US 01/22010		
C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.	
A	COBB J E ET AL: "N-(2-Benzoylphenyl)-L-tyrosine PPARgamma agonists. 3. Structure-activity relationship and optimization of the N-aryl substituent" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 25, 3 December 1998 (1998-12-03), pages 5055-5069, XP002156427 the whole document	***	1	
A	EP 0 930 299 A (JAPAN TOBACCO INC.) 21 July 1999 (1999-07-21) the whole document		1	
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INTERNATIONAL SEARCH REPORT

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Inte, Inal Application No
PCI/US 01/22616

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Form PCT/ISA/210 (patent family annex) (July 1992)

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Application No.: 10/700,417 Appeal Brief

CASE APPENDIX

Application No.: 10/700,417 Appeal Brief

CASE APPENDIX

- 1. Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459, 467 (1966)
- 2. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986)
- 3. Yamanouchi Pharmaceutical Co., Ltd. et al. v. Danbury Pharmacal, Inc. et al., 231 F.3d 1339, 1343 (Fed. Cir. 2000)
- 4. In re Mills, 916 F.2d 680, 682 (Fed. Cir. 1990)
- 5. Al-Site Corp. v. VSI Int'l Inc., 174 F3d 1308, 1324 (Fed. Cir. 1999)
- 6. In re Baird 16 F.3d 380, 383 (Fed. Cir. 1994)
- 7. In re Langer, 59 C.C.P.A. 1256, 1260, 465 F.2d 896, 899 (CCPA 1972)
- 8. In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992)
- 9. Ex parte Burtner and Brown, 121 U.S.P.Q. 345, 347 (Bd. of App. 1951)

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86 S.Ct. 684 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 U.S.P.Q. 459 (Cite as: 383 U.S. 1, 86 S.Ct. 684)

P

Briefs and Other Related Documents

Supreme Court of the United States William T. GRAHAM et al., Petitioners,

v.

JOHN DEERE COMPANY OF KANSAS CITY et al. CALMAR, INC., Petitioner,

v.

COOK CHEMICAL COMPANY. COLGATE-PALMOLIVE COMPANY, Petitioner,

v.
COOK CHEMICAL COMPANY.
Nos. 11, 37, 43.

Argued Oct. 14, 1965. Decided Feb. 21, 1966.

In a patent infringement action, the United States District Court for the Western District of Missouri, 216 F.Supp. 272, entered judgment for plaintiffs, and defendants appealed. The Court of Appeals, Eighth Circuit, reversed, 333 F.2d 529. In separate actions, plaintiffs sought declaration that patent was invalid and not infringed. The United States District Court for the Western District of Missouri, 220 F.Supp. 414, held that patent was valid and infringed and plaintiffs appealed. The Court of Appeals, Eighth Circuit, affirmed, 336 F.2d 110. Certiorari was granted in both cases. The Supreme Court, Mr. Justice Clark, held that provision of Patent Act pertaining to nonpatentability of invention because of obviousness was intended to codify judicial precedents embracing principle announced by Supreme Court as early as 1850, that while clear language of provision places emphasis on inquiry into obviousness general level of innovation necessary to sustain patentability remains the same, and that patents at issue were invalid because of obviousness of subject matter.

Judgment in patent infringement action affirmed; judgment in declaratory judgment actions reversed and remanded.

West Headnotes

11 Patents 16(1) 291k16(1) Most Cited Cases (Formerly 291k16, 291k18) Provision of Patent Act pertaining to nonpatentability of invention because of obviousness was intended to codify judicial precedents embracing principle announced by Supreme Court as early as 1850; and while clear language of provision places emphasis on inquiry into obviousness, general level of innovation necessary to sustain patentability remains the same. 35 U.S.C.A. § 103.

[2] Patents © 2

291k2 Most Cited Cases

Federal patent power stems from specific constitutional provision which authorizes Congress to promote progress of useful arts by securing for limited times to inventors exclusive right to their discoveries. U.S.C.A.Const. art. 1, § 8.

[3] Patents & 3

291k3 Most Cited Cases

Patent clause of <u>Article I of Constitution</u> is both grant of power and limitation. U.S.C.A.Const. art. 1, § 8.

[4] Patents @ 3

291k3 Most Cited Cases

Patent clause of <u>Article I of Constitution</u> is limited to promotion of advances in useful arts. U.S.C.A.Const. art. 1, § 8.

[5] Patents & 2

291k2 Most Cited Cases

Congress in exercise of patent power may not overreach restraints imposed by stated constitutional purpose to promote advances in useful arts nor may it enlarge patent monopoly without regard to innovation, advancement, or social benefit gained thereby, nor may it authorize issuance of patents whose effects are to remove existent knowledge from public domain or to restrict free access to materials already available. U.S.C.A.Const. art. 1, § 8.

[6] Patents 16(1)

291k16(1) Most Cited Cases

(Formerly 291k16)

Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in patent system which by constitutional command must promote progress of useful arts; such is the standard expressed in the Constitution and it may not be ignored. U.S.C.A.Const. art. 1, § 8.

383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 U.S.P.Q. 459

(Cite as: 383 U.S. 1, 86 S.Ct. 684)

[7] Patents \$\infty\$ 16(1)

291k16(1) Most Cited Cases

(Formerly 291k16)

Patent validity requires reference to standard written into Constitution. U.S.C.A.Const. art. 1, § 8.

[8] Patents 5

291k3 Most Cited Cases

Within limits of constitutional grant, Congress may implement stated purpose by selecting policy which in its judgment best effectuates constitutional aim. U.S.C.A.Const. art. 1, § 8.

[9] Patents © 3

291k3 Most Cited Cases

Congressional power to implement stated purpose of framers with respect to granting of patents by selecting policy which in its judgment best effectuates constitutional aim is but corollary to grant to Congress of any Article I power. U.S.C.A.Const. art. 1, § 8.

[10] Patents & 2

291k2 Most Cited Cases

Within scope established by Constitution, Congress may set out conditions and tests for patentability. U.S.C.A.Const. art. 1, § 8.

[11] Patents \$\infty\$ 16(1)

291k16(1) Most Cited Cases

(Formerly 291k16)

It is duty of commissioner of patents and of courts in administration of patent system to give effect to constitutional standard by appropriate application in each case of statutory scheme.

[12] Patents 16.10(2)

291k16.10(2) Most Cited Cases

(Formerly 291k16.11)

Clause of Patent Act pertaining to nonpatentability of invention because of obviousness declaring "patentability shall not be negatived by the manner in which the invention was made" eliminated any requirement for a "flash of genius". 35 U.S.C.A. § 103.

[13] Patents \$\infty\$ 16(1)

291k16(1) Most Cited Cases

(Formerly 291k16, 291k18)

Emphasis on nonobviousness in determining patentability is one of inquiry, not quality, and as such comports with constitutional strictures. 35 U.S.C.A. § 103; U.S.C.A.Const. art. 1, § 8.

[14] Patents 6 16.13

291k16.13 Most Cited Cases

Ultimate question of patent validity is one of law.

[15] Patents \$\infty\$ 16(2)

291k16(2) Most Cited Cases

(Formerly 291k18)

Under Patent Act provision pertaining nonobviousness as condition for patentability, scope and content of prior art are to be determined, differences between prior art and claims at issue are to be ascertained, and level of ordinary skill in pertinent art resolved; and against this background obviousness or nonobviousness of subject matter is determined. 35 U.S.C.A. § 103.

[16] Patents 36.1(1)

291k36.1(1) Most Cited Cases

(Formerly 291k18)

[16] Patents \$\infty\$ 36.1(3)

291k36.1(3) Most Cited Cases

(Formerly 291k16.7)

[16] Patents 36.2(1)

291k36.2(1) Most Cited Cases

(Formerly 291k36(2))

Such secondary considerations as commercial success, long-felt but unsolved needs, and failure of others, might be utilized to give light to circumstances surrounding origin of subject matter sought to be patented as indicia of obviousness or nonobviousness. 35 U.S.C.A. § 103.

[17] Patents @ 328(2)

291k328(2) Most Cited Cases

(Formerly 291k328)

2,627,798. Patent No. 2,627,798, relating to spring clamp which permitted plow shanks to be pushed upward when they struck obstructions in soil and to spring back into normal position when obstruction was passed over, was invalid because of obviousness of subject matter. 35 U.S.C.A. § 103.

[18] Patents 6 168(1)

291k168(1) Most Cited Cases

Invention is construed not only in light of claims but also with reference to file wrapper or prosecution history in patent office.

[19] Patents 168(2.2)

291k168(2.2) Most Cited Cases Cancellation.

383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 U.S.P.Q. 459 (Cite as: 383 U.S. 1, 86 S.Ct. 684)

(Formerly 291k168(21/4))

Claims as allowed must be read and interpreted with reference to rejected ones and to state of prior art, and claims that have been narrowed in order to obtain issuance of patent by distinguishing prior art cannot be sustained to cover that which was previously by limitation eliminated from patent.

[20] Patents \$\infty\$168(2.2)

291k168(2.2) Most Cited Cases

(Formerly 291k168(21/4))

Where patentee obtained patent only by accepting limitations imposed by patent examiner and claims were carefully drafted to reflect such limitations, broader view of invention could not thereafter be asserted.

[21] Patents \$\infty\$ 328(2)

291k328(2) Most Cited Cases

(Formerly 291k328)

2,870,943. Patent No. 2,870,943, relating to plastic finger sprayer with "hold down" lid used as built-in dispenser for containers or bottles packaging liquid products, principally household insecticides, was invalid because of obviousness of subject matter. 35 U.S.C.A. § 103.

Patents @ 328(4)

291k328(4) Most Cited Cases 1,447,712, 2,844,290, 2,118,222, 2,119,884, 2,493,811, 2,586,687, 2,751,480. Cited. **686 *2 No. 11:

Orville O. Gold, Kansas City, Mo., for petitioners.

S. Tom Morris, Amarillo, Tex., for respondents.

Nos. 37, 43:

Dennis G. Lyons, Washington, D.C., for petitioners.

Gordon D. Schmidt, Kansas City, Mo., for respondent.

*3 Mr. Justice CLARK delivered the opinion of the Court.

After a lapse of 15 years, the Court again focuses its attention on the patentability of inventions under the standard of Art. I, s 8, cl. 8, of the Constitution and under the conditions prescribed by the laws of the United States. Since our last expression on patent validity, Great A. & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 71 S.Ct. 127, 95 L.Ed.

162 (1950), the Congress has for the first time expressly added a third statutory dimension to the two requirements of novelty and utility that had been the sole statutory test since the Patent Act of 1793. This is the test of obviousness, i.e., whether 'the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.' s 103 of the Patent Act of 1952, 35 U.S.C. s 103 (1964 ed.).

[1] The questions, involved in each of the companion cases before us, are what effect the 1952 Act had upon traditional statutory and judicial tests of patentability and what definitive tests are now required. We have concluded that the 1952 Act was intended to codify judicial precedents embracing the principle long ago *4 announced by this Court in Hotchkiss v. Greenwood, 11 How. 248, 13 L.Ed. 683 (1851), and that, while the clear language of s 103 places emphasis on an inquiry into obviousness, the general **687 level of innovation necessary to sustain patentability remains the same.

I.

The Cases.

(a). No. 11, Graham v. John Deere Co., an infringement suit by petitioners, presents a conflict between two Circuits over the validity of a single patent on a 'Clamp for vibrating Shank Plows.' The invention, a combination of old mechanical elements. involves a device designed to absorb shock from plow shanks as they plow through rocky soil and thus to prevent damage to the plow. In 1955, the Fifth Circuit had held the patent valid under its rule that when a combination produces an 'old result in a cheaper and otherwise more advantageous way,' it is patentable. Jeoffroy Mfg., Inc. v. Graham, 219 F.2d 511, cert. denied, 350 U.S. 826, 76 S.Ct. 55, 100 L.Ed. 738. In 1964, the Eighth Circuit held, in the case at bar, that there was no new result in the patented combination and that the patent was, therefore, not valid. 333 F.2d 529, reversing D.C., 216 F.Supp. 272. We granted certiorari, <u>379 U.S. 956, 85 S.Ct. 652, 13 L.Ed.2d 553.</u> Although we have determined that neither Circuit applied the correct test, we conclude that the patent is invalid under s 103 and, therefore, we affirm the judgment of the Eighth Circuit.

(b). No. 37, Calmar, Inc. v. Cook Chemical Co., and No. 43, Colgate-Palmolive Co. v. Cook Chemical Co., both from the Eighth Circuit, were separate

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(Cite as: 383 U.S. 1, 86 S.Ct. 684)

declaratory judgment actions, but were filed contemporaneously. Petitioner in Calmar is the manufacturer of a finger-operated sprayer with a 'hold-down' cap of the type commonly seen on grocers' shelves inserted in bottles of insecticides and other liquids prior to shipment. Petitioner in Colgate-Palmolive is a purchaser of the sprayers and *5 uses them in the distribution of its products. Each action sought a declaration of invalidity and noninfringement of a patent on similar sprayers issued to Cook Chemical as assignee of Baxter I. Scoggin, Jr., the inventor. By cross-action, Cook Chemical claimed infringement. The actions were consolidated for trial and the patent was sustained by the District Court. 220 F.Supp. 414. The Court of Appeals affirmed, 8 Cir., 336 F.2d 110, and we granted certiorari, 380 U.S. 949, 85 S.Ct. 1082, 13 L.Ed.2d 967. We reverse.

Manifestly, the validity of each of these patents turns on the facts. The basic problems, however, are the same in each case and require initially a discussion of the constitutional and statutory provisions covering the patentability of the inventions.

II.

[2][3][4][5][6][7] At the outset it must be remembered that the federal patent power stems from a specific constitutional provision which authorizes the Congress 'To promote the Progress of * * * useful Arts, by securing for limited Times to * * * Inventors the exclusive Right to their * * * Discoveries.' Art. I, s 8, cl. 8. [FN1] The clause is both a grant of power and a limitation. This qualified authority, unlike the power often exercised in the sixteenth and seventeenth centuries by the English Crown, is limited to the promotion of advances in the 'useful arts.' It was against the backdrop of the written practices--eventually curtailed by the Statute of Monopolies--of the Crown in granting monopolies to court favorites in goods or businesses which had long before been enjoyed by the public. See Meinhardt, Inventions, Patents and Monopoly, pp. **688 30--35 (London, 1946). The Congress in the *6 exercise of the patent power may not overreach the restraints imposed by the stated constitutional purpose. Nor may it enlarge the patent monopoly without regard to the innovation, advancement or social benefit gained thereby. Moreover, Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available. Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must 'promote the Progress of * * * useful Arts.' This is the

standard expressed in the Constitution and it may not be ignored. And it is in this light that patent validity 'requires reference to a standard written into the Constitution.' Great A. & P. Tea Co. v. Supermarket Equipment Corp., supra, 340 U.S. at 154, 71 S.Ct. at 131 (concurring opinion).

FN1. The provision appears in the Constitution spliced together with the copyright provision, which we omit as not relevant here. See H.R.Rep.No.1923, 82d Cong., 2d Sess., at 4 (1952); DeWolf, An Outline of Copyright Law, p. 15 (Boston, 1925).

[8][9][10][11] Within the limits of the constitutional grant, the Congress may, of course, implement the stated purpose of the Framers by selecting the policy which in its judgment best effectuates the constitutional aim. This is but a corollary to the grant to Congress of any Article I power. Gibbons v. Ogden, 9 Wheat. 1, 6 L.Ed. 23. Within the scope established by the Constitution, Congress may set out conditions and tests for patentability. McClurg v. Kingsland, 1 How. 202, 206, 11 L.Ed. 102. It is the duty of the Commissioner of Patents and of the courts in the administration of the patent system to give effect to the constitutional standard by appropriate application, in each case, of the statutory scheme of the Congress.

Congress quickly responded to the bidding of the Constitution by enacting the Patent Act of 1790 during the second session of the First Congress. It created an agency in the Department of State headed by the Secretary of State, the Secretary of the Department of War *7 and the Attorney General, any two of whom could issue a patent for a period not exceeding 14 years to any petitioner that 'hath * * * invented or discovered any useful art, manufacture, * * * or device, or any improvement therein not before known or used' if the board found that 'the invention or discovery (was) sufficiently useful and important * * *.' 1 Stat. 110. This group, whose members administered the patent system along with their other public duties, was known by its own designation as 'Commissioners for the Promotion of Useful Arts.'

Thomas Jefferson, who as Secretary of State was a member of the group, was its moving spirit and might well be called the 'first administrator of our patent system.' See Federico, Operation of the Patent Act of 1790, 18 J.Pat.Off.Soc. 237, 238 (1936). He was not only an administrator of the patent system under the 1790 Act, but was also the author of the 1793 Patent Act. In addition, Jefferson was himself an inventor of

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great note. His unpatented improvements on plows, to mention but one line of his inventions, won acclaim and recognition on both sides of the Atlantic. Because of his active interest and influence in the early development of the patent system, Jefferson's views on the general nature of the limited patent monopoly under the Constitution, as well as his conclusions as to conditions for patentability under the statutory scheme, are worthy of note.

Jefferson, like other Americans, had an instinctive aversion to monopolies. It was a monopoly on tea that sparked the Revolution and Jefferson certainly did not favor an equivalent form of monopoly under the new government. His abhorrence of monopoly extended initially to patents as well. From France, he wrote to Madison (July 1788) urging a Bill of Rights provision restricting monopoly, and as against the argument that *8 limited **689 monopoly might serve to incite 'ingenuity,' he argued forcefully that 'the benefit even of limited monopolies is too doubtful to be opposed to that of their general suppression,' V Writings of Thomas Jefferson, at 47 (Ford ed., 1895).

His views ripened, however, and in another letter to Madison (Aug. 1789) after the drafting of the Bill of Rights, Jefferson stated that he would have been pleased by an express provision in this form:

'Art. 9. Monopolies may be allowed to persons for their own productions in literature, & their own inventions in the arts, for a term not exceeding _ _ years, but for no longer term & no other purpose.' Id., at 113.

And he later wrote:

'Certainly an inventor ought to be allowed a right to the benefit of his invention for some certain time. *

* * Nobody wishes more than I do that ingenuity should receive a liberal encouragement.' Letter to Oliver Evans (May 1807), V Writings of Thomas Jefferson, at 75--76 (Washington ed.).

Jefferson's philosophy on the nature and purpose of the patent monopoly is expressed in a letter to Isaac McPherson (Aug. 1813), a portion of which we set out in the margin. [FN2] He rejected a natural-rights theory in *9 intellectual property rights and clearly recognized the social and economic rationale of the patent system. The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge. The grant of an exclusive right to an invention was the creation of society--at odds with the inherent free nature of disclosed ideas--and was not to be freely given. Only inventions and discoveries which furthered human knowledge,

and were new and useful, justified the special inducement of a limited private monopoly. Jefferson did not believe in granting patents for small details, obvious improvements, or frivolous devices. His writings evidence his insistence upon a high level of patentability.

FN2. 'Stable ownership is the gift of social law, and is given late in the progress of society. It would be curious then, if an idea, the fugitive fermentation of an individual brain, could, of natural right, be claimed in exclusive and stable property. If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it. Its peculiar character, too, is that no one possesses the less, because every other possesses the whole of it. He who receives an idea from me. receives instruction himself without lessening mine; as he who lights his taper at mine, receives light without darkening me. That ideas should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature, when she made them, like fire, expansible over all space, without lessening their density in any point, and like the air in which we breathe, move, and have our physical being, incapable of confinement or exclusive appropriation. Inventions then cannot, in nature, be a subject of property. Society may give an exclusive right to the profits arising from them, encouragement to men to pursue ideas which may produce utility, but this may or may not be done, according to the will and convenience of the society, without claim or complaint from anybody.' VI Writings of Thomas Jefferson, at 180--181 (Washington ed.).

As a member of the patent board for several years, Jefferson saw clearly the difficulty in 'drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not.' The board on which he served sought to draw such a line and formulated several rules which

**690 are preserved in *10 Jefferson's correspondence. [FN3] Despite the board's efforts, Jefferson saw 'with what slow progress a system of general rules could be matured.' Because of the 'abundance' of cases and the fact that the investigations occupied 'more time of the members of the board than they could spare from higher duties, the whole was turned over to the judiciary, to be matured into a system, under which every one might know when his actions were safe and lawful.' Letter to McPherson, supra, at 181, 182. Apparently Congress agreed with Jefferson and the board that the courts should develop additional conditions for patentability. Although the Patent Act was amended, revised or codified some 50 times between 1790 and 1950, Congress steered clear of a statutory set of requirements other than the bare novelty and utility tests reformulated in Jefferson's draft of the 1793 Patent Act.

FN3. '(A) machine of which we are possessed, might be applied by every man to any use of which it is susceptible.' Letter to Isaac McPherson, supra, at 181.

'(A) change of material should not give title to a patent. As the making a ploughshare of cast rather than of wrought iron; a comb of iron instead of horn or of ivory * * *.' Ibid.

'(A) mere change of form should give no right to a patent, as a high-quartered shoe instead of a low one; a round hat instead of a three-square; or a square bucket instead of a round one.' Id., at 181--182.

'(A combined use of old implements.) A man has a right to use a saw, an axe, a plane separately; may he not combine their uses on the same piece of wood?' Letter to Oliver Evans, (Jan. 1814), VI Writings of Thomas Jefferson, at 298 (Washington ed.).

III.

The difficulty of formulating conditions for patentability was heightened by the generality of the constitutional grant and the statutes implementing it, together with the underlying policy of the patent system that 'the things which are worth to the public the embarrassment *11 of an exclusive patent,' as Jefferson put it, must outweigh the restrictive effect of the limited patent monopoly. The inherent problem was to develop some means of weeding out those inventions which would not be disclosed or devised but for the inducement of a patent.

This Court formulated a general condition of patentability in 1851 in <u>Hotchkiss v. Greenwood, 11 How. 248, 13 L.Ed. 683.</u> The patent involved a mere

substitution of materials--porcelain or clay for wood or metal in doorknobs--and the Court condemned it, holding: [FN4]

<u>FN4.</u> In historical retrospect, the specific result in Hotchkiss flows directly from an application of one of the rules of the original board of 'Commissioners,' n. 3, second rule, supra.

'(U)nless more ingenuity and skill * * * were required * * * than were possessed by an ordinary mechanic acquainted with the business, there was an absence of that degree of skill and ingenuity which constitute essential elements of every invention. In other words, the improvement is the work of the skilful mechanic, not that of the inventor.' At p. 267.

Hotchkiss, by positing the condition that a patentable invention evidence more ingenuity and skill than that possessed by an ordinary mechanic acquainted with the business, merely distinguished between new and useful innovations that were capable of sustaining a patent and those that were not. The Hotchkiss test laid the cornerstone of the judicial evolution suggested by Jefferson and left to the courts by Congress. The language in the case, and in those which followed, gave birth to 'invention' as a word of legal art signifying patentable inventions. Yet, as this Court has observed, '(t)he truth is, the word ('invention') cannot be defined in such manner as **691 to afford any substantial aid in determining whether a particular device involves an exercise of the inventive faculty *12 or not.' McClain v. Ortmayer, 141 U.S. 419, 427, 12 S.Ct. 76, 78, 35 L.Ed. 800 (1891); Great A. & P. Tea Co. v. Supermarket Equipment Corp., supra, 340 U.S., at 151, 71 S.Ct. at 129. Its use as a label brought about a large variety of opinions as to its meaning both in the Patent Office, in the courts, and at the bar. The Hotchkiss formulation, however, lies not in any label, but in its functional approach to questions of patentability. In practice, Hotchkiss has required a comparison between the subject matter of the patent, or patent application, and the background skill of the calling. It has been from this comparison that patentability was in each case determined.

IV.

The 1952 Patent Act.

The Act sets out the conditions of patentability in three sections. An analysis of the structure of these three sections indicates that patentability is dependent upon three explicit conditions: novelty and utility as

articulated and defined in s 101 and s 102, and nonobviousness, the new statutory formulation, as set out in s 103. The first two sections, which trace closely the 1874 codification, express the 'new and useful' tests which have always existed in the statutory scheme and, for our purposes here, need no clarification. [FN5] The pivotal *13 section around which the present controversy centers is s 103. It provides:

FN5. 's 101. Inventions patentable

'Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.'

's 102. Conditions for patentability; novelty and loss of right to patent

- 'A person shall be entitled to a patent unless-'(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
- '(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or
- '(c) he has abandoned the invention, or
- '(d) the invention was first patented or caused to be patented by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application filed more than twelve months before the filing of the application in the United States, or
- '(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or
- '(f) he did not himself invent the subject matter sought to be patented, or
- '(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice,

from a time prior to conception by the other.' The precursors of these sections are to be found in the Act of February 21, 1793, c. 11, 1 Stat. 318; Act of July 4, 1836, c. 357, 5 Stat. 117; Act of July 8, 1870, c. 230, 16 Stat. 198; Rev.Stat. s 4886 (1874).

's 103. Conditions for patentability; non-obvious subject matter

'A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention **692 was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.'

*14 The section is cast in relatively unambiguous terms. Patentability is to depend, in addition to novelty and utility, upon the 'non-obvious' nature of the 'subject matter sought to be patented' to a person having ordinary skill in the pertinent art.

The first sentence of this section is strongly reminiscent of the language in Hotchkiss. Both formulations place emphasis on the pertinent art existing at the time the invention was made and both are implicitly tied to advances in that art. The major distinction is that Congress has emphasized 'nonobviousness' as the operative test of the section, rather than the less definite 'invention' language of Hotchkiss that Congress thought had led to 'a large variety' of expressions in decisions and writings. In the title itself the Congress used the phrase 'Conditions for patentability; non-obvious subject matter' (italics added), thus focusing upon 'nonobviousness' rather than 'invention.' [FN6] The Senate and House Reports, S.Rep. No. 1979, 82d Cong., 2d Sess. (1952); H.R.Rep. No. 1923, 82d Cong., 2d Sess. (1952), U.S.Code Congressional and Administrative News 1952, p. 2394, reflect this emphasis in these terms:

FN6. The corresponding provision in the preliminary draft was titled 'Conditions for patentability, lack of invention' (italics added), Proposed Revision and Amendment of the Patent Laws, Preliminary Draft with Notes, House Committee on the Judiciary (Committee Print, 1950).

'Section 103, for the first time in our statute, provides a condition which exists in the law and has

existed for more than 100 years, but only by reason of decisions of the courts. An invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent. That has been expressed in a large variety of ways in decisions of *15 the courts and in writings. Section 103 states this requirement in the title. It refers to the difference between the subject matter sought to be patented and the prior art, meaning what was known before as described in section 102. If this difference is such that the subject matter as a whole would have been obvious at the time to a person skilled in the art, then the subject matter cannot be patented. 'That provision paraphrases language which has often been used in decisions of the courts, and the section is added to the statute for uniformity and definiteness. This section should have a stabilizing effect and minimize great departures which have appeared in some cases.' H.R.Rep., supra, at 7; S.Rep., supra, at 6.

[12] It is undisputed that this section was, for the first time, a statutory expression of an additional requirement for patentability, originally expressed in Hotchkiss. It also seems apparent that Congress intended by the last sentence of s 103 to abolish the test it believed this Court announced in the controversial phrase 'flash of creative genius,' used in Cuno Engineering Corp. v. Automatic Devices Corp., 314 U.S. 84, 62 S.Ct. 37, 86 L.Ed. 58 (1941). [FN7]

FN7. The sentence in which the phrase occurs reads: '(T)he new device, however useful it may be, must reveal the flash of creative genius not merely the skill of the calling.' At p. 91, 62 S.Ct. at p. 41. Although some writers and lower courts found in the language connotations as to the frame of mind of the inventors, none Hotchkiss specifically, and the reference to 'flash of creative genius' was but a rhetorical embellishment of language going back to 1833. Cf. 'exercise of genius,' Shaw v. Cooper, 7 Pet. 292, 8 L.Ed. 689; 'inventive genius,' Reckendorfer v. Faber, 92 U.S. 347, 23 L.Ed. 719 (1876); Concrete Appliance Co. v. Gomery, 269 U.S. 177, 46 S.Ct. 42, 70 L.Ed. 222; 'flash of thought,' Densmore v. Scofield, 102 U.S. 375, 26 L.Ed. 214 (1880); 'intuitive genius,' Potts v. Creager, 155 U.S. 597, 15 S.Ct. 194, 39 L.Ed. 275 (1895). Rather than establishing a more exacting

standard, Cuno merely rhetorically restated the requirement that the subject matter sought to be patented must be beyond the skill of the calling. It was the device, not the invention, that had to reveal the 'flash of creative genius.' See Boyajian, The Flash of Creative Genius, An Alternative Interpretation, 25 J.Pat.Off.Soc. 776, 780, 781 (1943); Pacific Contact Laboratories, Inc. v. Solex Laboratories, Inc., 9 Cir., 209 F.2d 529, 533; Brown & Sharpe Mfg. Co. v. Kar Engineering Co., 1 Cir., 154 F.2d 48, 51--52; In re Shortell, 142 F.2d 292, 295--296, 31 CCPA (Pat.) 1062, 1069.

**693 *16 It is contended, however, by some of the parties and by several of the amici that the first sentence of \underline{s} 103 was intended to sweep away judicial precedents and to lower the level of patentability. Others contend that the Congress intended to codify the essential purpose reflected in existing judicial precedents--the rejection of insignificant variations and innovations of a commonplace sort--and also to focus inquiries under \underline{s} 103 upon nonobviousness, rather than upon 'invention,' as a means of achieving more stability and predictability in determining patentability and validity.

The Reviser's Note to this section, [FN8] with apparent reference to Hotchkiss, recognizes that judicial requirements as to 'lack of patentable novelty (have) been followed since at least as early as 1850.' The note indicates that the section was inserted because it 'may have some stabilizing effect, and also to serve as a basis for the addition at a later time of some criteria which may be worked out.' To this same effect are the reports of both Houses, supra, which state that the first sentence *17 of the section 'paraphrases language which has often been used in decisions of the courts, and the section is added to the statute for uniformity and definiteness.'

FN8. There is no provision corresponding to the first sentence explicitly stated in the present statutes, but the refusal of patents by the Patent Office, and the holding of patents invalid by the courts, on the ground of lack of invention or lack of patentable novelty has been followed since at least as early as 1850. This paragraph is added with the view that an explicit statement in the statute may have some stabilizing effect, and also to serve as a basis for the addition at a later time of some criteria which may be worked out.

'The second sentence states that patentability

> as to this requirement is not to be negatived by the manner in which the invention was made, that is, it is immaterial whether it resulted from long toil and experimentation or from a flash of genius.'

We believe that this legislative history, as well as other sources, [FN9] shows that the revision was not intended by Congress to change the general level of patentable invention. We conclude that the section was intended merely as a codification of judicial precedents embracing the Hotchkiss condition, with congressional directions that inquiries into the obviousness of the subject matter sought to be patented are a prerequisite to patentability.

FN9. See Efforts to Establish a Statutory Standard of Invention, Study No. 7, Senate Subcommittee on Patents, Trademarks, and Copyrights, 85th Cong., 1st Sess. (Committee Print, 1958); Hearings, Subcommittee No. 3, House Committee on the Judiciary, on H.R. 3760, 82d Cong., 1st Sess. (1951).

V

[13] Approached in this light, the <u>s 103</u> additional condition, when followed realistically, will permit a more practical test of patentability. The emphasis on non-obviousness is one of inquiry, not **694 quality, and, as such, comports with the constitutional strictures.

[14][15][16] While the ultimate question of patent validity is one of law, Great A. & P. Tea Co. v. Supermarket Equipment Corp., supra, 340 U.S. at 155, 71 S.Ct. at 131, the s 103 condition, which is but one of three conditions, each of which must be satisfied, lends itself to several basic factual inquiries. Under s 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances *18 surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy. See Note, Subtests of 'Nonobviousness': A Nontechnical Approach to Patent Validity, 112 U.Pa.L.Rev. 1169 (1964).

This is not to say, however, that there will not be difficulties in applying the nonobviousness test. What is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context. The difficulties, however, are comparable to those encountered daily by the courts in such frames of reference as negligence and scienter, and should be amenable to a case-by-case development. We believe that strict observance of the requirements laid down here will result in that uniformity and definiteness which Congress called for in the 1952 Act.

While we have focused attention on the appropriate standard to be applied by the courts, it must be remembered that the primary responsibility for sifting out unpatentable material lies in the Patent Office. To await litigation is -- for all practical purposes -- to debilitate the patent system. We have observed a notorious difference between the standards applied by the Patent Office and by the courts. While many reasons can be adduced to explain the discrepancy, one may well be the free rein often exercised by Examiners in their use of the concept of 'invention.' In this connection we note that the Patent Office is confronted with a most difficult task. Almost 100,000 applications for patents are filed each year. Of these, about 50,000 are granted and the backlog now runs well over 200,000. 1965 Annual Report of the Commission of Patents 13--14. This is itself a compelling reason for the Commissioner to strictly adhere to the 1952 Act as interpreted here. This would, we believe, not only expedite disposition but *19 about a closer concurrence between administrative and judicial precedent. [FN10]

FN10. The President has appointed a Commission on the Patent System. Executive Order No. 11215, 30 Fed.Reg. 4661 (April 10, 1965). It is hoped that its studies may develop more efficient administrative procedures and techniques that will further expedite dispositions and at the same time insure the strict application of appropriate tests of patentability.

Although we conclude here that the inquiry which the Patent Office and the courts must make as to patentability must be beamed with greater intensity on the requirements of \underline{s} 103, it bears repeating that we find no change in the general strictness with which the overall test is to be applied. We have been urged to find in \underline{s} 103 a relaxed standard, supposedly a congressional reaction to the 'increased standard' applied by this Court in its decisions over the last 20 or 30 years. The standard has remained invariable in this

Court. Technology, however, has advanced--and with remarkable rapidity in the last 50 years. Moreover, the ambit of applicable art in given fields of science has widened by **695 disciplines unheard of a half century ago. It is but an evenhanded application to require that those persons granted the benefit of a patent monopoly be charged with an awareness of these changed conditions. The same is true of the less technical, but still useful arts. He who seeks to build a better mousetrap today has a long path to tread before reaching the Patent Office.

VI.

We now turn to the application of the conditions found necessary for patentability to the cases involved here:

A. The Patent in Issue in No. 11, Graham v. John Deere Co.

This patent, No. 2,627,798 (hereinafter called the '798 patent) relates to a spring clamp which permits plow shanks to be pushed upward when they hit obstructions *20 in the soil, and then springs the shanks back into normal position when the obstruction is passed over. The device, which we show diagrammatically in the accompanying sketches (Appendix, Fig. 1), is fixed to the plow frame as a unit. The mechanism around which the controversy center is basically a hinge. The top half of it, known as the upper plate (marked 1 in the sketches), is a heavy metal piece clamped to the plow frame (2) and is stationary relative to the plow frame. The lower half of the hinge, known as the hinge plate (3), is connected to the rear of the upper plate by a hinge pin (4) and rotates downward with respect to it. The shank (5), which is bolted to the forward end of the hinge plate (at 6), runs beneath the plate and parallel to it for about nine inches, passes through a stirrup (7), and then continues backward for several feet curving down toward the ground. The chisel (8), which does the actual plowing, is attached to the rear end of the shank. As the plow frame is pulled forward, the chisel rips through the soil, thereby plowing it. In the normal position, the hinge plate and the shank are kept tight against the upper plate by a spring (9), which is atop the upper plate. A rod (10) runs through the center of the spring, extending down through holes in both plates and the shank. Its upper end is bolted to the top of the spring while its lower end is hooked against the underside of the shank.

When the chisel hits a rock or other obstruction in the soil, the obstruction forces the chisel and the rear portion of the shank to move upward. The shank is

pivoted (at 11) against the rear of the hinge plate and pries open the hinge against the closing tendency of the spring. (See sketch labeled 'Open Position,' Appendix, Fig. 1.) This closing tendency is caused by the fact that, as the hinge is opened, the connecting rod is pulled downward and the spring is compressed. When the obstruction *21 is passed over, the upward force on the chisel disappears and the spring pulls the shank and hinge plate back into their original position. The lower, rear portion of the hinge plate is constructed in the form of a stirrup (7) which brackets the shank, passing around and beneath it. The shank fits loosely into the stirrup (permitting a slight up and down play). The stirrup is designed to prevent the shank from recoiling away from the hinge plate, and thus prevents excessive strain on the shank near its bolted connection. The stirrup also girds the shank, preventing it from fishtailing from side to side.

In practical use, a number of spring-hinge-shank combinations are clamped to a plow frame, forming a set of ground-working chisels capable of withstanding the shock of rocks and other obstructions in the soil without breaking the shanks.

Background of the Patent.

Chisel plows, as they are called, were developed for plowing in areas where the ground is relatively free from rocks or **696 stones. Originally, the shanks were rigidly attached to the plow frames. When such plows were used in the rocky, glacial soils of some of the Northern States, they were found to have serious defects. As the chisels hit buried rocks, a vibratory motion was set up and tremendous forces were transmitted to the shank near its connection to the frame. The shanks would break. Graham, one of the petitioners, sought to meet that problem, and in 1950 obtained a patent, U.S. No. 2,493,811 (hereinafter '811), on a spring clamp where solved some of the difficulties. Graham and his companies manufactured and sold the '811 clamps. In 1950, Graham modified the '811 structure and filed for a patent. That patent, the one in issue, was granted in 1953. This suit against competing plow manufacturers resulted from charges by petitioners that several of respondents' devices infringed the '798 patent.

*22 The Prior Art.

Five prior patents indicating the state of the art were cited by the Patent Office in the prosecution of the '798 application. Four of these patents, 10 other United States patents and two prior-use spring-clamp arrangements not of record in the '798 file wrapper

were relied upon by respondents as revealing the prior art. The District Court and the Court of Appeals found that the prior art 'as a whole in one form or another contains all of the mechanical elements of the 798 Patent.' One of the prior-use clamp devices not before the Patent Examiner--Glencoe--was found to have 'all of the elements.'

We confine our discussion to the prior patent of Graham, '811, and to the Glencoe clamp device, both among the references asserted by respondents. The Graham '811 and '798 patent devices are similar in all elements, save two: (1) the stirrup and the bolted connection of the shank to the hinge plate do not appear in '811; and (2) the position of the shank is reversed, being placed in patent '811 above the hinge plate, sandwiched between it and the upper plate. The shank is held in place by the spring rod which is hooked against the bottom of the hinge plate passing through a slot in the shank. Other differences are of no consequence to our examination. In practice the '811 patent arrangement permitted the shank to wobble or fishtail because it was not rigidly fixed to the hinge plate; moreover, as the hinge plate was below the shank, the latter caused wear on the upper plate, a member difficult to repair or replace.

Graham's '798 patent application contained 12 claims. All were rejected as not distinguished from the Graham '811 patent. The inverted position of the shank was specifically rejected as was the bolting of the shank to the hinge plate. The Patent Office examiner found these to be 'matters of design well within the expected skill of *23 the art and devoid of invention.' Graham withdrew the original claims and substituted the two new ones which are substantially those in issue here. His contention was that wear was reduced in patent '798 between the shank and the heel or rear of the upper plate. [FN11] He also emphasized several new features, the relevant one here being that the bolt used to connect the hinge plate and shank maintained the upper face of the shank in continuing **697 and constant contact with the underface of the hinge plate.

FN11. In '811, where the shank was above the hinge plate, an upward movement of the chisel forced the shank up against the underside of the rear of the upper plate. The upper plate thus provided the fulcrum about which the hinge was pried open. Because of this, as well as the location of the hinge pin, the shank rubbed against the heel of the upper plate causing wear both to the plate and to the shank. By relocating the hinge pin and by

placing the hinge plate between the shank and the upper plate, as in '798, the rubbing was eliminated and he wear point was changed to the hinge plate, a member more easily removed or replaced for repair.

Graham did not urge before the Patent Office the greater 'flexing' qualities of the '798 patent arrangement which he so heavily relied on in the courts. The sole element in patent '798 which petitioners argue before us is the interchanging of the shank and hinge plate and the consequences flowing from this arrangement. The contention is that this arrangement--which petitioners claim is not disclosed in the prior art--permits the shank to flex under stress for its entire length. As we have sketched (see sketch, 'Graham '798 Patent' in Appendix, Fig. 2), when the chisel hits an obstruction the resultant force (A) pushes the rear of the shank upward and the shank pivots against the rear of the hinge plate at (C). The natural tendency is for that portion of the shank between the pivot point and the bolted connection (i.e., between C and D) to bow downward and away from the hinge plate. The maximum distance (*24 B) that the shank moves away from the plate is slight--for emphasis, greatly exaggerated in the sketches. This is so because of the strength of the shank and the short--nine inches or so--length of that portion of the shank between (C) and (D). On the contrary, in patent '811 (see sketch, 'Graham '811 Patent' in Appendix, Fig. 2), the pivot point is the upper plate at point (c); and while the tendency for the shank to bow between points (c) and (d) is the same as in '798, the shank is restricted because of the underlying hinge plate and cannot flex as freely. In practical effect, the shank flexes only between points (a) and (c), and not along the entire length of the shank, as in '798. Petitioners say that this difference in flex, though small, effectively absorbs the tremendous forces of the shock of obstructions whereas prior art arrangements failed.

The Obviousness of the Differences.

[17] We cannot agree with petitioners. We assume that the prior art does not disclose such an arrangement as petitioners claim in patent '798. Still we do not believe that the argument on which petitioners' contention is bottomed supports the validity of the patent. The tendency of the shank to flex is the same in all cases. If free-flexing, as petitioners now argue, is the crucial difference above the prior art, then it appears evident that the desired result would be obtainable by not boxing the shank within the confines of the hinge. [FN12] The only other effective place available in the arrangement was

to attach it below the hinge plate and run it through a *25 stirrup or bracket that would not disturb its flexing qualities. Certainly a person having ordinary skill in the prior art, given the fact that the flex in the shank could be utilized more effectively if allowed to run the entire length of the shank, would immediately see that the thing to do was what Graham did, i.e., invert the shank and the hinge plate.

<u>FN12</u>. Even petitioners' expert testified to that effect:

'Q. Given the same length of the forward portion of the clamp * * * you would anticipate that the magnitude of flex (in '798) would be precisely the same or substantially the same as in 811, wouldn't you?

'A. I would think so.'

Petitioners' argument basing validity on the free-flex theory raised for the first time on appeal is reminiscent of Lincoln Engineering Co. of Illinois v. Stewart-Warner Corp., 303 U.S. 545, 58 S.Ct. 662, 82 L.Ed. 1008 (1938), where the Court called such an effort 'an afterthought. No such function * * * is hinted at in the specifications of the patent. If this were so vital an element in the functioning of the apparatus, it is strange that all mention of it was omitted.' At p. 550, 58 S.Ct. at p. 665. No 'flexing' argument **698 was raised in the Patent Office. Indeed, the trial judge specifically found that 'flexing is not a claim of the patent in suit * * *' and would not permit interrogation as to flexing in the accused devices. Moreover, the clear testimony of petitioners' experts shows that the flexing advantages flowing from the '798 arrangement are not, in fact, a significant feature in the patent. [FN13]

FN13. 'Q. * * * Do you regard the small degree of flex in the forward end of the shank that lies between the pivot point and the point of spring attachment to be of any significance or any importance to the functioning of a device such as 798? A. Unless you are approaching the elastic limit, I think this flexing will reduce the maximum stress at the point of pivot there, where the maximum stress does occur. I think it will reduce that. I don't know how much.

'Q. Do you think it is a substantial factor, a factor of importance in the functioning of the structure? A. Not a great factor, no.'

The same expert previously testified similarly in <u>Jeoffoy Mfg., Inc. v. Graham, 219 F.2d 511</u>.

We find no nonobvious facets in the '798 arrangement. The wear and repair claims were sufficient to overcome *26 the patent examiner's original conclusions as to the validity of the patent. However, some of the prior art, notably Glencoe, was not before him. There the hinge plate is below the shank but, as the courts below found, all of the elements in the '798 patent are present in the Glencoe structure. Furthermore, even though the position of the shank and hinge plate appears reversed in Glencoe, the mechanical operation is identical. The shank there pivots about the underside of the stirrup, which in Glencoe is above the shank. In other words, the stirrup in Glencoe serves exactly the same function as the heel of the hinge plate in '798. The mere shifting of the wear point to the heel of the '798 hinge plate from the stirrup of Glencoe--itself a part of the hinge plate--presents no operative mechanical distinctions, much less nonobvious differences.

B. The Patent in Issue in No. 37, Calmar, Inc. v. Cook Chemical Co., and in No. 43, Colgate-Palmolive Co. v. Cook Chemical Co.

The single patent [FN14] involved in these cases relates to a plastic finger sprayer with a 'hold-down' lid used as a built-in dispenser for containers or bottles packaging liquid products, principally household insecticides. Only the first two of the four claims in the patent are involved here and we, therefore, limit our discussion to them. We do not set out those claims here since they are printed in 220 F.Supp., at 417--418.

FN14. The patent is U.S. No. 2,870,943 issued in 1959 to Cook Chemical Co. as assignee of Baxter I. Scoggin, Jr., the inventor. In No. 37, Calmar is the manufacturer of an alleged infringing device, and, in No. 43, Colgate is a customer of Calmar and user of its device.

In essence the device here combines a finger-operated pump sprayer, mounted in a container or bottle by means of a container cap, with a plastic overcap which screws over the top of and depresses the sprayer (see Appendix, *27 Fig. 3). The pump sprayer passes through the container cap and extends down into the liquid in the container; the overcap fits over the pump sprayer and screws down on the outside of a collar mounting or retainer which is molded around the body of the sprayer. When the overcap is screwed down on this collar mounting a seal is formed by the engagement of a circular ridge or rib located above the threads on the collar mounting with a mating shoulder

located inside the overcap above its threads. [FN15] The overcap, as it is screwed down, depresses the pump plunger rendering the pump inoperable and when the seal is effected, **699 any liquid which might seep into the overcap through or around the pump is prevented from leaking out of the overcap. The overcap serves also to protect the sprayer head and prevent damage to it during shipment or merchandising. When the overcap is in place it does not reach the cap of the container or bottle and in no way engages it since a slight space is left between those two pieces.

FN15. Our discussion here relates to the overcap seal. The container itself is sealed in the customary way through the use of a container gasket located between the container and the container cap.

The device, called a shipper-sprayer in the industry, is sold as an integrated unit with the overcap in place enabling the insecticide manufacturer to install it on the container or bottle of liquid in a single operation in an automated bottling process. The ultimate consumer simply unscrews and discards the overcap, the pump plunger springs up and the sprayer is ready for use.

The Background of the Patent.

For many years manufacturers engaged in the insecticide business had faced a serious problem in developing sprayers that could be integrated with the containers or bottles in which the insecticides were marketed. Originally, insecticides were applied through the use of tin *28 sprayers, not supplied by the manufacturer. In 1947, Cook Chemical, an insecticide manufacturer, began to furnish its customers with plastic pump dispensers purchased from Calmar. The dispenser was an unpatented finger-operated device mounted in a perforated cardboard holder and hung over the neck of the bottle or container. It was necessary for the ultimate consumer to remove the cap of the container and insert and attach the sprayer to the latter for use.

Hanging the sprayer on the side of the container or bottle was both expensive and troublesome. Packaging for shipment had to be a hand operation, and breakage and pilferage as well as the loss of the sprayer during shipment and retail display often occurred. Cook Chemical urged Calmar to develop an integrated sprayer that could be mounted directly in a container or bottle during the automated filling process and that would not leak during shipment or retail handling. Calmar did develop some such devices

but for various reasons they were not completely successful. The situation was aggravated in 1954 by the entry of Colgate-Palmolive into the insecticide trade with its product marketed in aerosol spray cans. These containers, which used compressed gas as a propellent to dispense the liquid, did not require pump sprayers.

During the same year Calmar was acquired by the Drackett Company. Cook Chemical became apprehensive of its source of supply for pump sprayers and decided to manufacture its own through a subsidiary, Bakan Plastics, Inc. Initially, it copied its design from the unpatented Calmar sprayer, but an officer of Cook Chemical, Scoggin, was assigned to develop a more efficient device. By 1956 Scoggin had perfected the shipper-sprayer in suit and a patent was granted in 1959 to Cook Chemical as his assignee. In the interim Cook Chemical began to use Scoggin's device and also marketed *29 it to the trade. The device was well received and soon became widely used.

In the meanwhile, Calmar employed two engineers, Corsette and Cooprider, to perfect a shipper-sprayer and by 1958 it began to market its SS--40, a device very much similar to Scoggin's. When the Scoggin patent issued, Cook Chemical charged Calmar's SS--40 with infringement and this suit followed.

The Opinions of the District Court and the Court of Appeals.

At the outset it is well to point up that the parties have always disagreed as to the scope and definition of the invention claimed in the patent in suit. Cook Chemical contends that the invention encompasses a unique combination of admittedly old elements and that patentability is found in the result produced. Its expert testified that the invention was 'the first commercially successful, inexpensive integrated shipping closure pump unit which permitted automated assembly with a container of household **700 insecticide or similar liquids to produce a practical, ready-to-use package which could be shipped without external leakage and which was so organized that the pump unit with its hold-down cap could be itself assembled and sealed and then later assembled and sealed on the container without breaking the first seal.' Cook Chemical stresses the long-felt need in the industry for such a device; the inability of others to produce it; and its commercial success--all of which, contends Cook, evidences the nonobvious nature of the device at the time it was developed. On the other hand, Calmar says that the differences between Scoggin's shipper-sprayer

and the prior art relate only to the design of the overcap and that the differences are so inconsequential that the device as a whole would have been obvious at the time of its invention to a person having ordinary skill in the art.

*30 Both courts accepted Cook Chemical's contentions. While the exact basis of the District Court's holding is uncertain, the court did find the subject matter of the patent new, useful and nonobvious. It concluded that Scoggin 'had produced a sealed and protected sprayer unit which the manufacturer need only screw onto the top of its container in much the same fashion as a simple metal cap.' 220 F.Supp., at 418. Its decision seems to be bottomed on the finding that the Scoggin sprayer solved the long-standing problem that had confronted the industry. [FN16] The Court of Appeals also found validity in the 'novel 'marriage' of the sprayer with the insecticide container' which took years in discovery and in 'the immediate commercial success' which it enjoyed. While finding that the individual elements of the invention were 'not novel per se' the court found 'nothing in the prior art suggesting Scoggin's unique combination of these old features * * * as would solve the * * * problems which for years beset the insecticide industry.' It concluded that 'the * * * (device) meets the exacting standard required for a combination of old elements to rise to the level of patentable invention by fulfilling the long-felt need with an economical, efficient, utilitarian apparatus which achieved novel results and immediate commercial success.' 336 F.2d, at 114.

FN16. 'By the same reasoning, may it not also be said that if (the device) solved a long-sought need, it was likewise novel? If it meets the requirements of being new, novel and useful, it was the subject of invention, although it may have been a sort step, nevertheless it was the last step that ended the journey. The last step is the one that wins and he who takes it when others could not, is entitled to patent protection.' 220 F.Supp., at 421.

The Prior Art.

Only two of the five prior art patents cited by the Patent Office Examiner in the prosecution of Scoggin's application are necessary to our discussion, i.e., Lohse *31 U.S. Patent No. 2,119,884 (1938) and Mellon <u>U.S. Patent No. 2,586,687 (1952)</u>. Others are cited by Calmar that were not before the Examiner, but of these our purposes require discussion of only

the Livingstone <u>U.S. Patent No. 2,715,480 (1953)</u>. Simplified drawings of each of these patents are reproduced in the Appendix, Figs. 4--6, for comparison and description.

The Lohse patent (Fig. 4) is a shipper-sprayer designed to perform the same function as Scoggin's device. The differences, recognized by the District Court, are found in the overcap seal which in Lohse is formed by the skirt of the overcap engaging a washer or gasket which rests upon the upper surface of the container cap. The court emphasized that in Lohse '(t)here are no seals above the threads and below the sprayer head.' 220 F.Supp., at 419.

The Mellon patent (Fig. 5), however, discloses the idea of effecting a seal above the threads of the overcap. Mellon's device, likewise a shipper-sprayer, differs from Scoggin's in that its overcap **701 screws directly on the container, and a gasket, rather than a rib, is used to effect the seal.

Finally, Livingstone (Fig. 6) shows a seal above the threads accomplished without the use of a gasket or washer. [FN17] Although Livingstone's arrangement was designed to cover and protect pouring spouts, his sealing feature is strikingly similar to Scoggin's. Livingstone uses a tongue and groove technique in which the tongue, located on the upper surface of the collar, fits into a groove on the inside of the overcap. Scoggin employed the rib and shoulder seal in the identical position and with less efficiency because the Livingstone technique *32 is inherently a more stable structure, forming an interlock that withstands distortion of the overcap when subjected to rough handling. Indeed, Cook Chemical has now incorporated the Livingstone closure into its own shipper-sprayers as had Calmar in its SS--40.

FN17. While the sealing feature was not specifically claimed in the Livingstone patent, it was disclosed in the drawings and specifications. Under long-settled law the feature became public property. Miller v. Brass Co., 104 U.S. 350, 352, 26 L.Ed. 783 (1882).

The Invalidity of the Patent.

Let us first return to the fundamental disagreement between the parties. Cook Chemical, as we noted at the outset, urges that the invention must be viewed as the overall combination, or--putting it in the language of the statute--that we must consider the subject matter sought to be patented taken as a whole. With this

position, taken in the abstract, there is, of course, no quibble. But the history of the prosecution of the Scoggin application in the Patent Office reveals a substantial divergence in respondent's present position.

As originally submitted, the Scoggin application contained 15 claims which in very broad terms claimed the entire combination of spray pump and overcap. No mention of, or claim for, the sealing features was made. All 15 claims were rejected by the Examiner because (1) the applicant was vague and indefinite as to what the invention was, and (2) the claims were met by Lohse. Scoggin canceled these claims and submitted new ones. Upon a further series of rejections and new submissions, the Patent Office Examiner, after an office interview, at last relented. It is crystal clear that after the first rejection, Scoggin relied entirely upon the sealing arrangement as the exclusive patentable difference in his combination. It is likewise clear that it was on that feature that the Examiner allowed the claims. In fact, in a letter accompanying the final submission of claims, Scoggin, through his attorney, stated that 'agreement was reached between the Honorable Examiner and applicant's attorney relative to limitations which must be in the claims in *33 order to define novelty over the previously applied disclosure of Lohse when considered in view of the newly cited patents of Mellon and Darley, Jr.' (Italics added.)

Moreover, those limitations were specifically spelled out as (1) the use of a rib seal and (2) an overcap whose lower edge did not contact the container cap. Mellon was distinguished, as was the Darley patent, infra, n. 18, on the basis that although it disclosed a hold-down cap with a seal located above the threads, it did not disclose a rib seal disposed in such position as to cause the lower peripheral edge of the overcap 'to be maintained out of contacting relationship with (the container) cap * * * when * * * (the overcap) was screwed (on) tightly * * *.' Scoggin maintained that the 'obvious modification' of Lohse in view of Mellon would be merely to place the Lohse gasket above the threads with the lower edge of the overcap remaining in tight contact with the container cap or neck of the container itself. In other words, the **702 Scoggin invention was limited to the use of a rib--rather than a washer or gasket--and the existence of a slight space between the overcap and the container cap.

[18][19] It is, of course, well settled that an invention is construed not only in the light of the claims, but also with reference to the file wrapper or prosecution history in the Patent Office. Hogg v. Emerson, 11

How. 587, 13 L.Ed. 824 (1850); Crawford v. Heysinger, 123 U.S. 589, 8 S.Ct. 399, 31 L.Ed. 269 (1887). Claims as allowed must be read and interpreted with reference to rejected ones and to the state of the prior art; and claims that have been narrowed in order to obtain the issuance of a patent by distinguishing the prior art cannot be sustained to cover that which was previously by limitation eliminated from the patent. Powers-Kennedy Contracting Corp. v. Concrete Mixing & Conveying Co., 282 U.S. 175, 185--186, 51 S.Ct. 95, 99, 75 L.Ed. 278 (1930); Schriber-Schroth Co. v. Cleveland Trust Co., 311 U.S. 211, 220--221, 312 U.S. 654, 61 S.Ct. 235, 239--240, 85 L.Ed. 132 (1940).

*34 [20] Here, the patentee obtained his patent only by accepting the limitations imposed by the Examiner. The claims were carefully drafted to reflect these limitations and Cook Chemical is not now free to assert a broader view of Scoggin's invention. The subject matter as a whole reduces, then, to the distinguishing features clearly incorporated into the claims. We now turn to those features.

As to the space between the skirt of the overcap and the container cap, the District Court found:

'Certainly without a space so described, there could be no inner seal within the cap, but such a space is not new or novel, but it is necessary to the formation of the seal within the hold-down cap.

To me this language is descriptive of an element of the patent but not a part of the invention. It is too simple, really, to require much discussion. In this device the hold-down cap was intended to perform two functions—to hold down the sprayer head and to form a solid tight seal between the shoulder and the collar below. In assembling the element it is necessary to provide this space in order to form the seal.' 220 F.Supp. at 420. (Italics added.)

[21] The court correctly viewed the significance of that feature. We are at a loss to explain the Examiner's allowance on the basis of such a distinction. Scoggin was able to convince the Examiner that Mellon's cap contacted the bottle neck while his did not. Although the drawings included in the Mellon application show that the cap might touch the neck of the bottle when fully screwed down, there is nothing--absolutely nothing--which indicates that the cap was designed at any time to engage the bottle neck. It is palpably evident that Mellon embodies a seal formed by a gasket compressed *35 between the cap and the bottle neck. It follows that the cap in Mellon will not seal if it does not bear down on the gasket and this would be impractical, if not impossible, under the construction

urged by Scoggin before the Examiner. Moreover, the space so strongly asserted by Cook Chemical appears quite plainly on the Livingstone device, a reference not cited by the Examiner.

The substitution of a rib built into a collar likewise presents no patentable difference above the prior art. It was fully disclosed and dedicated to the public in the Livingstone patent. Cook Chemical argues, however, that Livingstone is not in the pertinent prior art because it relates to liquid containers having pouring spouts rather than pump sprayers. Apart from the fact that respondent made no such objection to similar **703 references cited by the Examiner, [FN18] so restricted a view of the applicable prior art is not justified. The problems confronting Scoggin and the insecticide industry were not insecticide problems; they were mechanical closure problems. Closure devices in such a closely related art as pouring spouts for liquid containers are at the very least pertinent references. See, II Walker on Patents s 260 (Deller ed. 1937).

FN18. In addition to Livingstone and Mellon, the Examiner cited Slade, <u>U.S. Patent No. 2,844,290</u> (hold-down cap for detergent cans having a pouring spout); Nilson, U.S. Patent No. 2,118,222 (combined cap and spout for liquid dispensing containers); Darley, Jr., U.S. Patent No. 1,447,712 (containers for toothpaste, cold creams and other semi-liquid substances).

Chemical insists, however, that the development of a workable shipper-sprayer eluded Calmar, who had long and unsuccessfully sought to solve the problem. And, further, that the long-felt need in the industry for a device such as Scoggin's together with its wide commercial success supports its patentability. These legal inferences *36 or subtests do focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible of judicial treatment than are the highly technical facts often present in patent litigation. See Judge Learned Hand in Reiner v. I. Leon Co., 285 F.2d 501, 504 (2 Cir. 1960). See also Note, Subtests of 'Nonobviousness': A Nontechnical Approach to Patent Validity, 112 U.Pa.L.Rev. 1169 (1964). Such inquiries may lend a helping hand to the judiciary which, as Mr. Justice Frankfurter observed, is most ill-fitted to discharge the technological duties cast upon it by patent legislation. Marconi Wireless Telegraph Co. of America v. United States, 320 U.S. 1, 60, 63 S.Ct.

1393, 87 L.Ed. 1731 (1943). They may also serve to 'guard against slipping into use of hindsight,' Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co., 332 F.2d 406, 412 (1964), and to resist the temptation to read into the prior art the teachings of the invention in issue.

However, these factors do not, in the circumstances of this case, tip the scales of patentability. The Scoggin invention, as limited by the Patent Office and accepted by Scoggin, rests upon exceedingly small and quite non-technical mechanical differences in a device which was old in the art. At the latest, those differences were rendered apparent in 1953 by the appearance of the Livingstone patent, unsuccessful attempts to reach a solution to the problems confronting Scoggin made before that time became wholly irrelevant. It is also irrelevant that no one apparently chose to avail himself of knowledge stored in the Patent Office and readily available by the simple expedient of conducting a patent search--a prudent and nowadays common preliminary to well organized research. Mast, Foos & Co. v. Stover Mfg. Co., 177 U.S. 485, 20 S.Ct. 708, 44 L.Ed. 856 (1900). To us, the limited claims of the Scoggin patent are clearly evident from the prior art as it stood at the time of the invention.

*37 We conclude that the claims in issue in the Scoggin patent must fall as not meeting the test of \underline{s} 103, since the differences between them and the pertinent prior art would have been obvious to a person reasonably skilled in that art.

The judgment of the Court of Appeals in No. 11 is affirmed. The judgment of the Court of Appeals in Nos. 37 and 43 is reversed and the cases remanded to the District Court for disposition not inconsistent with this opinion. It is so ordered.

Judgment of Court of Appeals in No. 11 affirmed. Judgment of Court of Appeals in Nos. 37 and 43 reversed and cases remanded to District Court.

Mr. Justice STEWART took no part in the consideration or decision of Nos. 37 and 43.

Mr. Justice FORTAS took no part in the consideration or decision of these cases.

APPENDIX TO OPINION OF THE COURT. FIGURE 1.-GRAHAM '798 PATENT

383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 U.S.P.Q. 459

(Cite as: 383 U.S. 1, 86 S.Ct. 684)

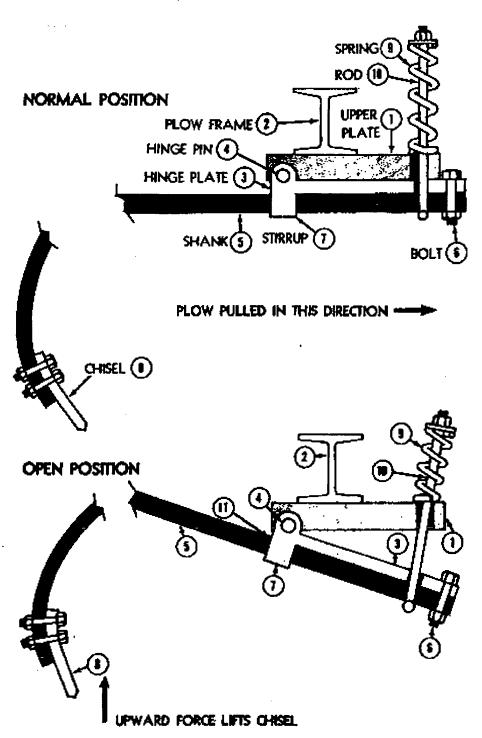
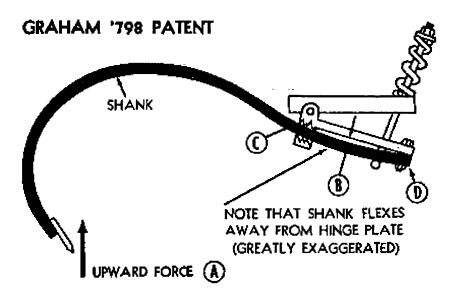


FIGURE 2.-FLEX COMPARISON

383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 U.S.P.Q. 459

(Cite as: 383 U.S. 1, 86 S.Ct. 684)



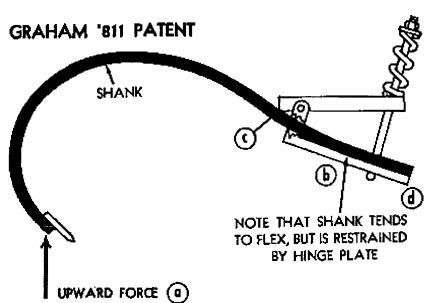


FIG. 3. SCOGGIN PATENT 2,870,943

383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 U.S.P.Q. 459

(Cite as: 383 U.S. 1, 86 S.Ct. 684)

(The Patent in Issue)

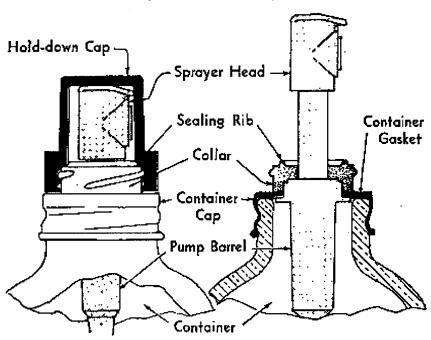


FIG. 5. MELLON <u>PATENT 2,586,687</u> (Prior art 1952)

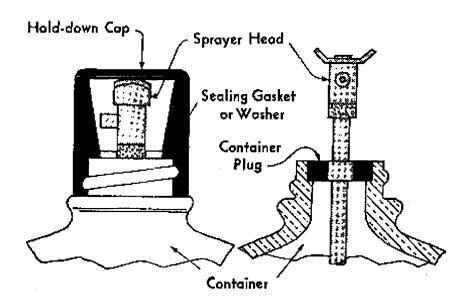
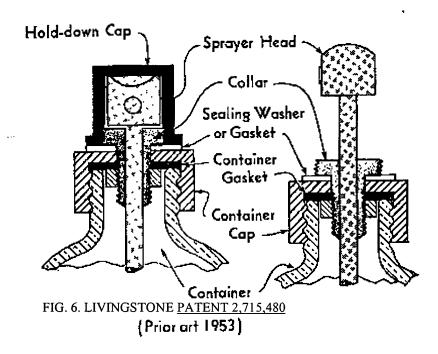
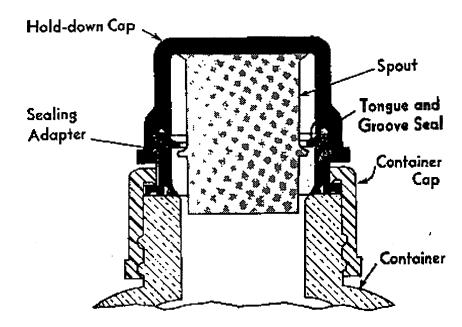


FIG. 4. LOHSE PATENT 2,119,884

(Prior art 1938)





Briefs and Other Related Documents (Back to top)

- <u>1965 WL 115658</u> (Appellate Brief) Brief for Respondent (Sep. 22, 1965)
- <u>1965 WL 115659</u> (Appellate Brief) Brief for Petitioner (Aug. 23, 1965)
- 1965 WL 115657 (Appellate Brief) Brief on Behalf of Respondents (Mar. 30, 1965)
- 1965 WL 115656 (Appellate Brief) Brief for the New York Patent Law Association as Amicus Curiae (Mar. 04, 1965)

- 1965 WL 115655 (Appellate Brief) Brief Amicus Curiae in Support of 35 USC 103 (Mar. 02, 1965)
- 1965 WL 115654 (Appellate Brief) Amicus Curiae Brief Of The Patent, Trade-Mark And Copyright Section Of The State Bar Of Texas (With The Consent Of The Board Of Directors Of The State Bar Of Texas) (Feb. 26, 1965)

END OF DOCUMENT

Westlaw.

786 F.2d 1136

786 F.2d 1136, 229 U.S.P.Q. 182

(Cite as: 786 F.2d 1136)

H

United States Court of Appeals,
Federal Circuit.
Milton HODOSH and Richardson-Vicks, Inc.,
Appellants,

BLOCK DRUG COMPANY, INC., et al., Appellees. Appeal No. 85-2607.

March 24, 1986.

Owner and licensee of patent describing method of desensitizing teeth brought infringement action. The United States District Court for the District of New Jersey, H. Lee Sarokin, J., granted summary judgment to defendant, and plaintiffs appealed. The Court of Appeals, Rich, Circuit Judge, held that genuine issue of material fact existed with respect to meaning of various terms used in Chinese and European references, precluding summary judgment on ground of obviousness.

Reversed and remanded.

West Headnotes

[1] Patents \$\infty\$16(2) 291k16(2) Most Cited Cases

[1] Patents 72(1)
291k72(1) Most Cited Cases
(Formerly 291k72)

Whether a reference is available as prior art and whether it anticipates, i.e., contains every claimed element, are separate questions. 35 U.S.C.A. §§ 102, 102(b).

[2] Patents 323.2(2)

291k323.2(2) Most Cited Cases

In infringement action brought by owner and licensee of patent describing method of desensitizing teeth, genuine issues of material fact

existed with respect to meaning of various terms used in Chinese and European references, precluding summary judgment on ground of obviousness of the claimed invention. 35 U.S.C.A. § 103.

[3] Patents \$\infty\$ 36.1(1)

291k36.1(1) Most Cited Cases

Evidence of secondary considerations is to be considered in patent infringement suit independently of what any real person knows about the prior art; these considerations are objective criteria of obviousness that help eliminate subjective determination involved in hypothesis used to draw legal conclusion of obviousness. 35 U.S.C.A. § 103.

Patents € 328(2)

291k328(2) Most Cited Cases 2,122,483, 3,863,006. Cited.

*1136 John O. Tramontine, Fish & Neave, of New York City, argued for appellant, Richardson-Vicks, Inc.

Hugh A. Chapin, Kenyon & Kenyon of New York City, argued for appellant, Milton *1137 Hodosh. With them on the brief were W. Edward Bailey and Norman H. Beamer of Fish & Neave and Paul Lempel and William J. McNichol, Jr. of Kenyon & Kenyon.

Jerome G. Lee, Morgan, Finnegan, Pine, Foley & Lee, of New York City, argued for appellees. With him on brief were William S. Feiler and Maria C.H. Lin of Morgan, Finnegan, Pine, Foley & Lee, and Marvin C. Soffen and Edward A. Meilman, Ostrolenk, Faber, Gerb & Soffen.

Before RICH, DAVIS, and BALDWIN, Circuit Judges.

RICH, Circuit Judge.

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(Cite as: 786 F.2d 1136)

This appeal is from the July 12, 1985, judgment of the United States District Court for the District of New Jersey, 226 USPQ 645, granting summary judgment to Block Drug Company, Inc., et al. (Block) and holding that all six claims of patent No. 3,863,006 for "Method of Desensitizing Teeth" ('006 patent), issued to Dr. Milton Hodosh and licensed to Richardson-Vicks, Inc. (collectively, Hodosh), are invalid for obviousness under 35 U.S.C. § 103. We reverse and remand.

Background

Tooth desensitizers reduce discomfort and pain caused by tooth hypersensitivity or exposed dentin, the portion of the tooth between the enamel and the pulp which includes a myriad of microscopic tubules. Persons suffering from this condition react painfully to hot or cold foods, citric acid or sweets, or everyday chemical, thermal, or tactile stimuli including toothbrush contact.

Milton Hodosh, a practicing dentist for about thirty years, independently developed the claimed subject of the '006 patent and granted Richardson-Vicks an exclusive license to make, use, and sell the claimed invention; the latter markets its tooth desensitizing toothpaste under the trademark "Denguel."

Claim 1 of the '006 patent [FN1] reads:

FN1. A certificate of reexamination confirming the patentability of claims 1-6 of the '006 patent was issued June 21, 1983, as a result of Hodosh's request for reexamination in 1982. Only one of the prior art references involved here, the Rosenthal patent, infra, was considered in the reexamination.

The method of desensitizing hypersensitive dentin and cementum by applying thereto an agent the essential ingredient of which is a nitrate of one of the following alkali metals: potassium, lithium or sodium said nitrate comprising between 1 percent and 20 percent by weight of

The remaining claims appear in the opinion below.

Appellee Block has, since 1961, marketed a tooth desensitizing toothpaste, covered by its patent No. 2,122,483 (the Rosenthal patent) for "Strontium Ion Toothpaste" issued in 1964, under the trademark "Sensodyne." The Rosenthal patent and the '006 patent disclose toothpaste formulae which are the same except that the latter contains, as a desensitizing agent, potassium nitrate instead of the Rosenthal-Block strontium chloride. requesting and being denied a license under the '006 patent, Block developed its own potassium nitrate-containing tooth-desensitizing toothpaste called "Promise" and "Sensodyne-F." [FN2]

> FN2. Block also initiated regulatory proceedings designed to delay or prevent Richardson-Vicks' marketing "Denquel." Block, having allegedly failed to comply with Food and Administration (FDA) procedures before marketing "Promise" and "Sensodyne-F" competitive response Richardson-Vicks' introduction of "Denquel," is currently defending itself in forfeiture proceedings initiated by the FDA.

March 30, 1983, Hodosh sued Block alleging that the sale of "Promise" and "Sensodyne-F" contributorily infringed and actively induced infringement of the '006 patent. Block answered and counterclaimed alleging patent misuse and consequent unenforceability of the '006 patent. On July 11, 1984, Block moved for summary judgment as to both misuse and patent invalidity. Oral argument was heard October 16, 1984, and decision was reserved. June 14, 1985, *1138 the reported decision was handed down granting the motion as to patent invalidity and dismissing the motion on misuse as moot, resulting in the judgment now on appeal.

The district court heard no expert testimony, but did hear arguments of counsel, receive briefs, review exhibits, and had before it declarations and affidavits from experts on both sides commenting on the eight prior art references involved here, including the Rosenthal patent. The court determined that there were no genuine issues of

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material fact and concluded as a matter of law that the claims of the '006 patent were invalid under § 103 because the Rosenthal patent disclosed each element claimed in the '006 patent except the potassium nitrate, which, in its view, was disclosed in two Chinese references, both based on ancient Chinese writings. The court also stated that six European references supported its conclusion of obviousness.

Because the appropriateness of summary judgment is determined on an analysis of the facts, First National Bank of Arizona v. Cities Service Co., 391 U.S. 253, 88 S.Ct. 1575, 20 L.Ed.2d 569 (1968), and because everything about these references, as a whole, see, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547-48 (Fed.Cir.1985), is important to our determination, we review the record and lay out the relevant portions of the references in some detail.

A. The Chinese References 1. The Grand Dictionary of Chinese Medicine and Drugs

(The Grand Dictionary)

The Grand Dictionary, published in Hong Kong in 1963 and written in Chinese, is based on ancient Chinese compilations assembled roughly 500 years ago from works of physicians going back 4000-5000 years. Only a portion of the 1963 Chinese text was before the court and is before us on appeal. For purposes of this litigation, that portion was translated into English by Block's translator, Roger Wei-Ming Tsao (Mr. Cao). Mr. Cao is a doctor of Chinese medicine and a bilingual tutor. Block's other expert, Dr. Stephen Wei, a professor of dentistry fluent in Chinese, concurred in that translation. The writings from which the Grand Dictionary was compiled are not in evidence nor are any earlier writings.

In a nutshell, the district court relied upon the Grand Dictionary because of its discussion of "xiao shi" to which the Grand Dictionary associates the name "niter" and the chemical composition KNO₃ and the ability to cure, inter alia, tooth pain. The court's opinion was that this reference teaches the use of xiao shi, which is the same as niter and is

therefore the same as potassium nitrate, to cure tooth pain; thus, the teachings of the Rosenthal patent and the Grand Dictionary show that the '006 invention would have been obvious.

The following discussion and quotations are part of an attempt to convey the nature of the Grand Dictionary. The translated portion of the Grand Dictionary is entitled "Niter." The text under the first subheading "Nomenclature" reads: "It was so named because it has the power to consume various stones." Under "Other Names Stated in Classical Medical Books," the text reads "Mang Xiao (Bie-Lu), Bitter Xiao (Zhen-Quan), Flaming Xiao (Tu-Su) ... and Xiao-Shi" Thereafter, following "Foreign Names," the *Grand Dictionary* reads: "Salpetrae, Salnitri (in Latin); Niter (in English); and Salpoter (in German)." One page later, "KNO3 " is listed under "Chemical Composition."

The portion upon which Block and the district court rely to show that this substance cures tooth pain is headed "Collective Statements" and reads:

(Ming): Li-Shi-Zhen said: It cures summer infections and the catching of colds. It cures acute enteritis with severe vomiting, exertion through excessive sexual activity, black jaundice, chronic abdominal pain, conjunctivitis, headaches and tooth pain.

The next three or so pages of the Grand Dictionary list the ailments that this substance cures. An interesting but not atypical *1139 paragraph reads: "For curing the paralysis of the four limbs, leprosy or problems caused by Taoist stone eating." This substance also apparently cures indigestion, lack of energy, typhoid, cataracts, and much, much more. The Grand Dictionary compares what appears to be various forms in which xiao shi is found, and the characteristics of each. An excerpt is:

Pu-Xiao (Na₂SO₄) has the nature of water, tastes salty, and its flavor is cold. It can only descend and cannot ascend. It is Yin within Yin--that's why it can cleanse the accumulation in the gastrointestinal tract and can expel the San-Jiao devilish fire. Whereas Niter (KNO3) has the nature of fire, tastes bitter and spicy, tastes slightly salty and has a flavor which is very warm,

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it's [sic] nature is ascending. It is fire within water. That's why it can break the accumulation and disperse hardness, and cure the febrile diseases.

2. Ben Cao Gang Mu

Ben Cao Gang Mu (Ben Cao) is a treatise on Chinese Medicine published in Hong Kong, in Chinese, in 1930, 1954, and 1965, but was originally written by Li-Shi-Zhen who lived during the Ming Dynasty. [FN3] Like the Grand Dictionary, only a portion of the Chinese text Ben Cao is in evidence and that portion was translated by Mr. Cao and Dr. Wei for purposes of this litigation. The district court relied upon Ben Cao because it discusses "xiao shi," which the translation of Ben Cao states is "niter" and associates the ability to cure "tooth pain (Ya Tong or Ya Teng)."

FN3. The Ming Dynasty (1368-1644 AD) was marked by the restoration of traditional institutions in China and the development of the arts, especially in porcelain, textiles, and painting.

It is important to note, and the district court appeared to accept as fact, that the portion of the *Grand Dictionary* relied upon was compiled during the Ming Dynasty of the 13th to 15th centuries in *Ben Cao Gang Mu* so that the relevant portion of the *Grand Dictionary* is substantially a restatement of *Ben Cao* with some modification by an unidentified author. The court stated that these two references "quote the same Ming Dynasty source as labeling KNO₃ for tooth pain."

The *Ben Cao* translation is entitled "Xiao-Shi (Niter)" and refers to the same "Other names" for this substance listed in the *Grand Dictionary*. With respect to the quoted sections above, the *Ben Cao* translation is nearly verbatim. It has this to say about tooth pain:

Da Ming states: It cures summer infections and the catching of colds, acute enteritis with severe vomiting, exertion thru excessive sexual activity and black jaundice, chronic abdominal pain, conjunctivitis, headache and tooth pain (Ya-Tong or Ya Teng).

Hodosh argues that summary judgment was inappropriate; issues of fact as to the meanings of xiao shi and ya tong remain because a skilled dental researcher would surely seek and obtain a complete translation of the *Grand Dictionary* and of the other ancient Chinese references and would read those references carefully. Hodosh also argues that the ancient references should be dismissed because a person skilled in the art would find them incredible and would regard them as a quagmire of medical and dental nonsense. It therefore takes issue with the court's holding quoted below which apparently precluded inquiry into the accuracy of the references by one skilled in the art:

[A]ttacks upon the translation leading up to the prior art reference embodied in the *Grand Dictionary of Chinese Medicine and Drugs, ...* or upon Chinese medicine as a whole, ... are not here regarded as particularly pertinent, since they require skill beyond the scope of the "experienced researcher in dental fields...."

Hodosh relies heavily on its expert's, Dr. Shklar's, testimony about the Chinese references: "[T]hey represent in modern terms, materials that are rarely comprehensible and frequently contradictory in their literal terms. The materials are largely *1140 seen by contemporary medical scientists as absurd; no serious medical researcher would waste his or her time with them." [FN4] Hodosh also contests this holding by the district court:

FN4. Dr. Shklar is the Charles A. Brackett Professor of Oral Pathology at the Harvard School of Dental Medicine, and is an acclaimed expert in dentistry. He is also an expert on the history of dentistry and holds membership in the American Academy of the History of Dentistry.

Nor, if it is true that KNO₃ alleviates tooth sensitivity, is such reference in the prior art rebutted by the existence of errors in the reference such as, for example, the claim that KNO₃ is a cure for "exertion through excessive sexual activity." Whatever the merits of the

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other aspects of the Chinese references, the fact that they reveal KNO₃ to be a cure for ya tong is what is dispositive here. The reference clearly discloses such function of potassium nitrate, albeit in the context of otherwise incredible, and even erroneous descriptions of the compound's quality.

With respect to the specific meaning of xiao shi as used in these references, both Dr. Shklar and Hodosh's other expert, Mr. Yen, a professional translator of Chinese and English languages, stated that the compiler of the Grand Dictionary erred in associating potassium nitrate or niter with xiao shi. Mr. Yen states that he

was not able to render one single precise version because various dictionaries contain different and even conflicting definitions. For example, Source of Words, a Chinese language dictionary, published by Commercial Press, Taiwan, which has editions dating back to 1915, defines "Xiao-Shi" as "Mang-Xiao" on page 1255, and under "Mang-Xiao" on page 1770, reference is made that "Mang-Xiao" is "Liu-Suen-Na," and on page 1523 "Liu-Suen-Na" is defined as sodium sulfate (Na₂SO₄10H₂0).

Mr. Yen also stated that "Xiao-Shi could be more than one material and that more than one material may be represented by the term 'Xiao-Shi'."

Dr. Shklar concurred:

In my opinion, therefore, the answer to the question: What was "Xiao-Shi," is that it represented many different materials which cannot be identified with certainty.

Thus, these Exhibits did not describe potassium nitrate to one skilled in the art any more than any of the hundreds of salts, ores and oxides that possess some of the enumerated properties.

In addition, Dr. Shklar stated: "It is insufficient to simply state, as the Block translator does, that 'Xiao-Shi' is 'niter,' and then cite a modern dictionary to 'establish' that 'niter' is potassium nitrate." With respect to both the Grand Dictionary and Ben Cao, he stated that "the translator appears to have inserted the term 'niter' into the text where

the phrase 'consumer of stones' actually belongs."

Block's arguments, on the other hand, in part based on the short affidavit by Mr. Wei, substantially follow the district court's opinion. Block also challenges the competence of Hodosh's experts stating that they "either had no knowledge or training in the Chinese language or Chinese medicine or were unfamiliar with dentistry or medicine generally." Block also emphasizes that the Chinese references correctly disclose many of potassium nitrate's characteristics, like burning with a violet flame, useability for making signal fires and gun powder, and its water solubility; these three properties of xiao shi in the Chinese references definitely confirm, according to Block, that xiao shi is potassium nitrate, KNO₃.

B. The European Prior Art

This art is contained in six references and was not relied upon to any significant degree by Block or the district court. Hodosh scarcely mentions it on appeal, instead preferring to show the existence of genuine issues of material fact with respect to the Chinese references. After concluding that using potassium nitrate to cure tooth pain would have been obvious from Rosenthal in *1141 view of the Chinese art, the court stated: "Such holding is strengthened by the European prior art which, while ambiguous because of the several conflicting definitions in the term 'niter,' at least suggest to one skilled in the art that potassium nitrate ought to be tried as a cure for tooth pain in general."

Block submitted no affidavits that addressed the substance of the European references. Hodosh's Dr. Shklar, on the other hand, stated why this art, part of the "humors, spirits and Alchemy of the Dark Ages" having whatever medicinal effect they did by virtue of their use of wine, opium, or other narcotic substances, would have been questioned by one skilled in the art. He specifically contends that Block's translation of "nitre" is erroneous: "it is common knowledge that these terms meant sodium carbonate and/or carbonate-sodium sodium bicarbonate mixture....'

To afford a glimpse of the nature of these

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references, an interesting and typical excerpt, one quoted by the district court, based upon a statement by the long since deceased French surgeon Guy de Chauliac reads that "a mixture of 'cuttlebone, small white sea shells, pumice, burnt stag's horn, nitre, alum, rock salt, burnt roots of iris, aristolochia, and reeds' could create an effective dentifrice." (District court's emphasis.) Three of the European references are based on that statement. The district court noted the others:

Additionally, a 1693 treatise by the British Professor of Physics William Salmon states that nitrum "held in the Mouth ... immediately helps the Toothach, if burnt and used in a Dentifrice, it cleanses and whitens the Teeth." ... Similarly, a reference work by Hardianus a Mynsicht, translated into English in 1682, describes a mixture, including "nitre" as a "tincture for the toothache." ... Finally, Pliny the Elder, in his Historie of the World, The Second Tome, translated into English in 1601, describes the use of nitre to "easeth the toothach, if the mouth and gums be washed therwith," or if burned, as a dentifrice. [Reference to Exhibits omitted.]

With this description of both the Chinese and European references, and of what they represent as a whole, in hand, we consider the proper application of the *Graham* standards and their effect upon the propriety of summary judgment in this case. *See generally Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 693-94, 15 L.Ed.2d 545 (1966); *Panduit Corp. v. Dennison Manufacturing Co.*, 774 F.2d 1082, 227 USPQ 337 (Fed.Cir.1985).

OPINION

A. Summary Judgment

Summary judgment, in patent as in other cases, is appropriate where there is no genuine issue of material fact, and the movant is entitled to judgment as a matter of law. See Molinaro v. Fannon/Courier Corp., 745 F.2d 651, 653-54, 223 USPQ 706, 707 (Fed.Cir.1984). The movant bears the burden of demonstrating the absence of all genuine issues of material fact, and the district court must view the evidence in a light most favorable to the nonmoving party and draw all reasonable inferences in its favor. See United States v.

Diebold, Inc., 369 U.S. 654, 655, 82 S.Ct. 993, 994, 8 L.Ed.2d 176 (1962); Palumbo v. Don-Joy Co., 762 F.2d 969, 973, 226 USPQ 5, 7 (Fed.Cir.1985). The party opposing summary judgment must show an evidentiary conflict on the record; mere denials or conclusory statements are not sufficient. Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd., 731 F.2d 831, 836, 221 USPQ 561, 564 (Fed.Cir.1984). Summary judgment is authorized where it is quite clear what the truth is. Sartor v. Arkansas Natural Gas Corp., 321 U.S. 620, 627, 64 S.Ct. 724, 728-29, 88 L.Ed. 967 (1944).

B. The Issues Below

The decision and opinion of the district court granting summary judgment dealt with two issues: the first was whether the '006 patent is invalid as anticipated under § 102(b), the court holding it is not; *1142 and the second was whether the '006 patent is invalid for obviousness under § 103, the court holding that it is. Hodosh of course appeals the summary judgment with respect to only the issue on which it lost--obviousness--and Block has not appealed. Because we are remanding for trial, however, we will comment briefly on anticipation to make it clear that we deem that question to have been conclusively disposed of in this case and because it is closely related to the obviousness issue.

1. Anticipation, § 102(b)

We agree entirely with the district court's holding that the '006 patent is not invalid as anticipated because there is no issue of fact that none of the prior art references discloses every element of the claimed invention. This issue was, therefore, appropriately and properly disposed of by summary judgment.

[1] We do not agree, however, with some of the district court's remarks about anticipation, in particular, that the unavailability of the Chinese references and whether one skilled in the art could locate them with "reasonable diligence" bears on whether those references anticipate the claimed subject matter. Whether a reference is available as prior art and whether it anticipates (i.e., contains every claimed element) are separate questions. Moreover, the district court's determination that the

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references are unavailable for § 102 purposes seems to be inconsistent with the approach subsequently taken by the district court in determining obviousness. The court later used these same references to support its holding that the claimed subject matter would have been obvious at the time the invention was made to one of ordinary skill in the art.

2. Obviousness, § 103

[2] Questions of material fact remain with respect to the meaning of various terms used in the Chinese and European references and we therefore hold that summary judgment on the ground of obviousness of the claimed invention was improper.

The district court's statement that ya tong means tooth hypersensitivity as well as tooth pain is the resolution of a head-on factual controversy. The court improperly drew the inference against Hodosh, the nonmoving party, that a statement about ya tong made to the German Patent Office by Dr. Hodosh's German Patent Office by Dr. Hodosh's German patent agent was made with knowledge of the Chinese references. statement in question occurred seven years after the '006 patent issued in connection with Dr. Hodosh's counterpart German application. The statement was: "The supersensitivity of dentine has been known for a long time and can be traced back 4000 years to the Chinese where it was known as 'Ya Tong'." Hodosh in this suit disclaims this statement urging that it was factual error.

There is no evidence that the above statement was based on the Chinese references or that Dr. Hodosh conveyed this information to the German patent agent. The important fact question as to the meaning of ya tong cannot be overcome simply by styling this statement an admission binding on Hodosh. Hodosh is entitled, as Block essentially concedes, to rebut the statement with evidence to the contrary. Hodosh will have that chance at trial.

Nor does the statement in the affidavit of Block's expert, Dr. Wei, that ya tong means tooth hypersensitivity eliminate the presence of the question of the meaning of ya tong. As the Supreme Court long ago observed, "Experience has shown that opposite opinions of persons professing to be experts, may be obtained to any amount Winans v. New York and Erie Railroad Co., 21 How. 88, 62 U.S. 88, 16 L.Ed. 68 (1859). The substance of Dr. Skhlar's affidavit on behalf of Hodosh goes far beyond merely denying that ya tong means tooth hypersensitivity and thus is more than adequate to show an evidentiary conflict on the record with respect to this crucial point, thus precluding summary judgment. Cf. Union Carbide Corp. v. American Can Co., 724 F.2d 1567, 1571, 220 USPQ 584, 587-88 (Fed.Cir.1984).

*1143 Furthermore, a genuine issue of material fact exists with respect to the meaning of the terms nitre, nitrum, and nitri as used in the European references. Dr. Shklar's affidavit is more than adequate to withstand the challenge of this summary judgment motion. A reasonable inference that these terms are sodium, as opposed to potassium, compounds is permissible; Hodosh has shown an evidentiary conflict on the record. The European references, Dr. Shklar explained in his affidavit, are based on the 77 A.D. writings of Pliny The Elder, who understood these terms to mean "sodium carbonate and/or a sodium carbonate-sodium bicarbonate mixture."

The obviousness determination here, given the existence of genuine material issues of fact with respect to the meanings of terms used in these references, is not suitably disposed of by summary judgment under the rules pertaining thereto. See generally Palumbo, supra, and Lemelson v. TRW, Inc., 760 F.2d 1254, 1260-61, 225 USPQ 697, 700-01 (Fed.Cir.1985). The fact issues herein must be resolved by trial in which the conflicting views of the experts will be subject to the refining fire of cross examination, a more effective means of arriving at the legal conclusion of obviousness vel non than perusal of ex parte affidavits and declarations of partisan experts lobbed at each other from opposing trenches.

We observe, for the benefit of the trial court, that we are totally unimpressed by Block's forensic device of comparing the Rosenthal prior art

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toothpaste formula and the Hodosh toothpaste example in parallel columns and then asserting, as though it were filled with significant meaning, that the "only difference is the use of potassium nitrate in place of strontium chloride," or that "the Hodosh patent merely substitutes potassium nitrate for strontium chloride." This device was pushed to the limit in oral argument by pointing out that the Hodosh toothpaste has the same formula, except for the active desensitizing ingredient, down to the last decimal point. This argument is meaningless on the obviousness issue. "Sensodyne" and apparently other desensitizing toothpaste formulae being well known as commercial products, it is entirely clear that Dr. Hodosh's invention was the discovery of an apparently superior desensitizing agent and he never thought it was a toothpaste formula. He made that invention even if it should later be decided that it was known to the Chinese. It is apparent that Hodosh's patent solicitor merely adopted the prior art Rosenthal toothpaste base formula as a convenient example to illustrate the kind of a paste in which the Hodosh desensitizer might be used, which was within his right. The similarities-- indeed, identity--of the paste bases is irrelevant in considering the issue of the unobviousness of the desensitizer. The Rosenthal patent, cited as prior art by Hodosh in his patent specification, was the jumping-off place for the description of his discovery. Hodosh does not claim to have been the first inventor of a desensitizing toothpaste; he claims to have improved it. The issue for trial is whether his improvement would have been obvious. [FN5]

> FN5. Our comments on the district court's obviousness determination generally include the following tenets of patent law that must be adhered to when applying § 103: (1) the claimed invention must be considered as a whole (35 U.S.C. § 103; see, e.g., Jones v. Hardy, 727 F.2d 1524, 220 USPQ 1529, 1021, (Fed.Cir.1984) (though the difference between claimed invention and prior art may seem slight, it may also have been the key to advancement of the art)); (2) the references must be considered as a whole

and suggest the desirability and thus the obviousness of making the combination (see, e.g., Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed.Cir.1984)); (3) the references must be viewed without the benefit of hindsight vision afforded by the claimed invention (e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed.Cir.1983)); (4) "ought to be tried" is not the standard with which obviousness is determined (Jones. supra, 727 F.2d at 1530, 220 USPO at 1026); and (5) the presumption of validity remains constant and intact throughout litigation (35 U.S.C. § 285; e.g., American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1359-60, 220 USPQ 763, 770 (Fed.Cir.1984)).

C. Secondary Considerations

[3] The district court refused on the motion for summary judgment to consider *1144 the evidence of secondary considerations. After acknowledging its existence and the arguments based on it, it stated:

However, the court continues to find that the Hodosh patent is invalid on grounds of obviousness; these secondary considerations stem not from the novelty or inventiveness engendered by substituting potassium nitrate in an already existing formula, but from a lack of knowledge on the part of those in the field of the references here cited. That lack is here overcome by the presumption of omniscience discussed, supra, a rule of law by which the court is bound, whatever its merits.

That secondary considerations are not considered unless there is evidence that those in the industry knew of the prior art is a non sequitur. Evidence of considerations secondary is considered independently of what any real person knows about the prior art. These considerations are objective criteria of obviousness that help illuminate the subjective determination involved in the hypothesis used to draw the legal conclusion of obviousness

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based upon the first three factual inquiries delineated in Graham. Thus, to require that actual inventors in the field have the omniscience of the hypothetical person in the art is not only contrary to case law, see Kimberly-Clark v. Johnson & Johnson, 745 F.2d 1437, 223 USPQ 603 (Fed.Cir.1984), but

eliminates a useful tool for trial judges faced with a nonobviousness determination.

The secondary consideration evidence of record and the additional evidence likely to be submitted at trial must be considered in the obviousness determination. See generally Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1557, 225 USPQ 26, 32 (Fed.Cir.1985).

Conclusion

The grant of summary judgment of invalidity is reversed and the case is remanded for trial in accordance with this opinion.

REVERSED AND REMANDED.

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END OF DOCUMENT

Westlaw.

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Briefs and Other Related Documents

United States Court of Appeals, Federal Circuit. YAMANOUCHI PHARMACEUTICAL CO., LTD., Plaintiff-Appellee, and Merck & Co., Inc., Plaintiff-Appellee,

DANBURY PHARMACAL, INC., Schein Pharmaceutical, Inc., and Marsam Pharmaceuticals, Inc., Defendants-Appellants. No. 99-1521.

Decided Nov. 3, 2000 Rehearing and Rehearing En Banc Denied Dec. 14,

Owner of patent for anti-ulcer drug famotidine brought infringement action against competitor, who had filed Abbreviated New Drug Application (ANDA) for generic version. The United States District Court for the Southern District of New York, Richard Owen, Senior Judge, 21 F.Supp.2d 366, held for owner and awarded attorney fees. On appeal, the Court of Appeals, Rader, Circuit Judge, held that: (1) patent was not invalid as obvious, and (2) filing of baseless ANDA warranted award of attorney fees.

Affirmed.

West Headnotes

[1] Patents 291 \$\infty\$ 16(1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16 Invention and Obviousness in General

291k16(1) k. In General. Most Cited

Cases

Patents 291 \$\iinspec 36.1(1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k36 Weight and Sufficiency

291k36.1 Secondary Factors Affecting

Invention or Obviousness

291k36.1(1) k. In General. Most

Cited Cases

Factors relevant to determination of whether patent is invalid due to obviousness are: (1) scope and content of prior art, (2) differences between prior art and claimed invention, (3) level of skill in art, and (4) objective indicia of nonobviousness. 35 U.S.C.A. § 103.

[2] Patents 291 € 16.25

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.25 k. Chemical Compounds. Most

Cited Cases

For chemical compound, prima facie case of patent obviousness requires structural similarity between claimed and prior art subject matter, where prior art gives reason or motivation to make claimed compositions. 35 U.S.C.A. § 103.

[3] Patents 291 \$\iiin\$ 36.2(1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness 291k36 Weight and Sufficiency

291k36.2 Commercial Success

291k36.2(1) k. In General. Most

Cited Cases

Reasonable expectation of success, not absolute predictability, supports conclusion of patent obviousness. 35 U.S.C.A. § 103.

[4] Patents 291 \$\infty\$16.25

291 Patents

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291II Patentability 291II(A) Invention; Obviousness 291k16.25 k. Chemical Compounds. Most

Patent for anti-ulcer drug famotidine was not invalid due to obviousness absent showing that one of skill in art would have found motivation to combine piece from one chemical compound in prior art patent with piece of another compound in second prior art patent, and to then alter resulting intermediate compound to create famotidine. 35 U.S.C.A. § 103.

[5] Patents 291 € 313

291 Patents

291XII Infringement 291XII(C) Suits in Equity 291k313 k. Dismissal Before Hearing. Most Cited Cases

Patent invalidity claimant was not deprived of right to be fully heard, on patentee's motion for judgment as matter of law, even though claimant was not allowed to examine inventor; claimant had had opportunity to depose inventor, but chose not to do so, inventor's proposed testimony would have contradicted testimony of claimant's expert, and inventor's proposed testimony would not have been to dispositive issue. Fed.Rules relevant Civ.Proc.Rule 52(c), 28 U.S.C.A.

[6] Federal Courts 170B € 830

170B Federal Courts 170BVIII Courts of Appeals 170BVIII(K) Scope, Standards, and Extent 170BVIII(K)4 Discretion of Lower Court 170Bk830 k. Costs, Attorney's Fees and Other Allowances. Most Cited Cases Court of Appeals reviews district court's decision to award attorney fees under abuse of discretion standard, under which decision is affirmed unless it is clearly unreasonable, arbitrary, or fanciful, or based on erroneous conclusion of law or fact.

[7] Patents 291 249.1

291 Patents 291XII Infringement

291XII(A) What Constitutes Infringement 291k249 Patents for Compositions of Matter

291k249.1 k. In General. Most Cited

Cases

Abbreviated New Drug Application (ANDA) filer may infringe prescription drug manufacturer's patent without engaging in any actual commercial activities; mere act of filing ANDA can constitute infringement. 35 U.S.C.A. § 271(e)(2).

[8] Patents 291 325.11(3)

291 Patents

291XII Infringement 291XII(C) Suits in Equity 291k325 Costs 291k325.11 Disbursements in General 291k325.11(2) Attorney Fees 291k325.11(3) k. Award to

Plaintiff. Most Cited Cases Generic drug manufacturer's filing of unjustified Abbreviated New Drug Application (ANDA), asserting invalidity of ulcer drug manufacturer's patent, as well as its misconduct in ensuing litigation, warranted finding that case exceptional one justifying award of attorney fees. Federal Food, Drug, and Cosmetic Act, § 505(j)(2)(A)(iv), 21 U.S.C.A. § 355(j)(2)(A)(iv); 35 U.S.C.A. §§ 271(e), 285.

Patents 291 328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents 291k328 Patents Enumerated 291k328(2) k. Original Utility. Most Cited Cases

4,165,378, 4,252,819. Cited As Prior Art.

Patents 291 328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents 291k328 Patents Enumerated 291k328(2) k. Original Utility. Most Cited Cases

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4,283,408. Valid; Infringed.

*1340 Robert L. Baechtold, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiff-appellees. With him on the brief were Hugh C. Barrett, Brian V. Slater, William E. Solander, and Amr O. Aly. On the brief for Merck & Co., Inc., were Paul D. Matukaitis and William Krovatin, of Merck & Co., Inc., of Rahway, New Jersey. Also on the brief for Merck & Co., Inc., were John F. Lynch, Nicolas G. Barzoukas, and Gerard M. Devlin, Jr., Arnold, White & Durkee, of Houston, Texas.

William A. Alper, Cohen, Pontani, Lieberman & Pavane, of New York, New *1341 York, argued for defendants-appellants. With him on the brief were Thomas C. Pontani, Michael C. Stuart, Myron Cohen, Julia S. Kim, and Martin B. Pavane.

James F. Hurst, Winston & Strawn, of Chicago, Illinois, for amicus curiae National Pharmaceutical Alliance. Of counsel was Christine J. Siwik.

Before NEWMAN, RADER, and GAJARSA, Circuit Judges.

RADER, Circuit Judge.

On a motion for judgment as a matter of law (JMOL), the United States District Court for the Southern District of New York upheld the validity of claim 4 of U.S. Patent No. 4,283,408 (the '408 patent) in favor of Yamanouchi Pharmaceutical Co., Ltd. and Merck & Co., Inc. (collectively, Yamanouchi). See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 21 F.Supp.2d 366, 370, 48 USPQ2d 1741, 1744 (S.D.N.Y.1998). The district court also found that defendants Danbury Pharmacal, Inc. (Danbury), Schein Pharmaceutical, Inc. (Schein), and Marsam Pharmaceuticals, Inc. (Marsam) willfully infringed the '408 patent and awarded attorney fees to Yamanouchi. See id. at 378. Because the district court correctly upheld the validity of the '408 patent and did not abuse its discretion in awarding attorney fees, this court affirms.

The '408 patent, issued to Yamanouchi on August 11, 1981, relates to inhibitors of gastric acid secretion. Claim 4 of the '408 patent, the only claim at issue, claims famotidine for treating heartburn and ulcers. Famotidine belongs to a class of compounds known as histamine2 antagonists (H2 antagonists), which inhibit production of stomach acid. As Figure 1 illustrates, the general chemical structure of H2 antagonists includes a "substituted heterocycle" group, a "alkyl containing" chain (called a "bridge"), and a "polar tail," connected in that order:

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Figure 1 – Famotidine

Figure 1*----Famotidine

During the 1960s and 70s, drug manufacturers searched for H2 antagonists with improved pharmacological properties, including low toxicity, high activity, and lack of side effects. Research revealed hundreds of thousands of potential compounds. Indeed, pharmaceutical companies synthesized more than 11,000 H2 antagonist compounds. See Yamanouchi, 21 F.Supp.2d at 371 . Very rarely, however, were these compounds pharmacologically suitable H2 antagonists. Notable failures include tiotidine, which caused cancer in rats; burimamide, which was ineffective for oral dosing; metiamide, which caused white cell loss; lupitidine, which caused pre-cancerous lesions in rats; and oxmetidine, which caused hepatitis.

Of the 11,000 candidates for suitable compounds, fewer than fifty showed enough promise to warrant human clinical trials. Ultimately, the FDA approved only *1342 four for consumer use: cimetidine, FN1 ranitidine, FN2 famotidine, FN3 and nizatidine. FN4 Famotidine, the claimed compound at issue, has been extremely successful. In 1996, for example, prescription sales of famotidine in the United States alone reached over 690 million dollars.

FN1. The FDA approved cimetidine in 1977; SmithKline Beecham sells it as TAGAMET®.

FN2. The FDA approved ranitidine in 1983; Glaxo-Wellcome sells it as ZANTAC®.

FN3. The FDA approved famotidine in 1986; Merck sells it as PEPCID®).

FN4. The FDA approved nizatidine in 1988; Eli Lilly sells it as AXID®.

Danbury is a subsidiary of Schein, which produces and markets generic drugs. In January 1997, Danbury filed an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration (FDA) seeking approval to market generic famotidine. Under the ANDA procedure, an applicant seeks FDA approval to market a generic drug. The Hatch-Waxman Act, also known as The Drug Price Competition and Patent Term Restoration Act, Pub.L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 and 35 U.S.C. § 271(e) (1994)), amended the Federal Food, Drug, and Cosmetic Act (FDCA), Pub.L. No. 52-675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-397 (1994)), to permit filing of an ANDA to expedite FDA approval of a generic version of a drug previously approved by the FDA. See, e.g., Bayer AG v. Elan Pharm, Research Corp., 212 F.3d 1241, 1244, 54 USPO2d 1711, 1712 (Fed.Cir.2000).

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Under the FDCA, an ANDA filer must certify one of the following four statements concerning the previously approved drug: it is not patented (paragraph I certification), its patent has expired (paragraph II certification), its patent soon will expire on a specified date (paragraph III certification), or its patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug" covered by the ANDA (paragraph IV certification). See 21 U.S.C. 355(j)(2)(A)(vii)(I)-(IV). To obtain approval of an ANDA, the FDCA requires only that the generic drug is the "bioequivalent" of the previously approved drug. See 21 U.S.C. § 355(j)(2)(A)(iv).

In Danbury's ANDA for famotidine, Danbury made a paragraph IV certification that claim 4 of the '408 patent is invalid. See 21 U.S.C. 355(j)(2)(A)(vii)(IV). As the statute requires, Danbury, on March 26, 1997, sent Yamanouchi a Patent Certification Notice Letter. certification letter informed Yamanouchi Danbury's IV ANDA paragraph filing. Accompanying the certification letter were affidavits from Drs. Bernard Loev and John K. Siepler supporting Danbury's invalidity certification. The Notice Letter contained, as the statute requires, an analysis of the prior art and the reasons for the asserted invalidity.

Within forty-five days of receiving the certification letter, Yamanouchi filed suit against Danbury alleging infringement of the '408 patent under 35 U.S.C. § 271(e)(2)(A), and willful infringement under 35 U.S.C. § 285 (1994). See 35 U.S.C. § 271(e)(4). During this period, Marsam filed a number of paragraph IV ANDAs seeking FDA approval to market injectable versions of famotidine. Yamanouchi then filed suit against Marsam, and the two suits were consolidated (Danbury, Schein, and Marsam are hereinafter collectively referred to as Danbury). The parties agreed to a bench trial.

After Danbury presented its last witness on obviousness, Yamanouchi moved for JMOL under Fed.R.Civ.P. 52(c) (Rule 52(c)). With that motion, Yamanouchi argued that Danbury had not shown by clear and convincing evidence that claim 4 of the

'408 patent would have been obvious at the time of invention. The district court granted Yamanouchi's JMOL motion. See Yamanouchi, 21 F.Supp.2d at 370. Specifically, the district court found that Danbury had not shown any motivation to combine selected portions of various prior art compounds to create the specific compound famotidine and to obtain its extraordinary*1343 properties. See id. at 373. The district court characterized Danbury's case for obviousness as largely hindsight, speculation, and argument without an adequate foundation. See id. at 370, 373, 376. Based on those findings, the district court determined that Danbury willfully infringed the '408 patent. The district court thus found the case "exceptional" and awarded attorney fees and costs to Yamanouchi. See id. at 378.

II.

To grant a JMOL under Rule 52(c), a district judge must weigh the evidence and resolve credibility. See Fed.R.Civ.P. 52(a) and (c); Lemelson v. United States, 752 F.2d 1538, 1547, 224 USPQ 526, 530-31 (Fed.Cir.1985). Therefore, this court reviews the district court's JMOL findings as if entered at the conclusion of all the evidence. See Lemelson, 752 F.2d at 1547; Woods v. North Am. Rockwell Corp., 480 F.2d 644, 645-46 (10th Cir.1973). This court reviews the conclusion on obviousness, a question of law, without deference, and the underlying findings of fact for clear error. See Univ. of Colo. Found., Inc. v. Am. Cyanamid Co., 196 F.3d 1366, 1370, 52 USPO2d 1801, 1803 (Fed.Cir.1999).

A.

[1] [2] [3] Obviousness rests on several critical factual underpinnings: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention, (3) the level of skill in the art, and (4) the objective indicia of nonobviousness. See Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-67, 1 USPQ2d 1593, 1595-96 (Fed.Cir.1987); Graham v. John Deere Co., 383 U.S. 1, 17, 86 S.Ct. 684, 15

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L.Ed.2d 545 (1966). For a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions." In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed.Cir.1990) (en banc). "[A] reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness. In re Longi, 759 F.2d 887, 896, 225 USPQ 645, 651-52 (Fed.Cir.1985).

As noted earlier, the district court discerned that Danbury had not proven any motivation to combine prior art references to produce the claimed invention. This court has recently reemphasized the importance of the motivation to combine:

As this court has stated, "virtually all [inventions] are combinations of old elements." Therefore, an examiner [or accused infringer] may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner [or accused infringer] to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.

... To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In re Rouffet, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed.Cir.1998) (internal citations omitted).

[4] At the heart of this validity dispute is whether one of skill in this art would have found motivation to combine pieces from one compound in a prior art patent with a piece of another compound in the second prior art patent through a series of manipulations. According to Danbury, one of skill

in the art would have considered it obvious to select the example 44 compound from Yamanouchi's U.S. Patent No. 4,252,819 (the '819 patent) and tiotidine from the '378 patent to use as leads for making *1344 famotidine. These compounds, respectively, are three and eleven times more active than cimetidine-the benchmark compound at the time of invention (Figure 2). After selecting these two lead compounds, Danbury continues, it would have been obvious to combine the polar tail from example 44 (Figure 3) with the substituted heterocycle from tiotidine (Figure 4), thus creating the intermediate compound (Figure 5). Thereafter, to create famotidine, Danbury argues that it would have been obvious to perform a bioisosteric substitution of the carbamoyl (CONH2) group in the intermediate compound with a sulfamoyl group (SO2NH2).

Figure 2* ----Cimetidine

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Figure 2 - Cimetidine

Figure 3 - Example 44

Figure 3* ----Example 44

Figure 4* ----Tiotidine

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Figure 4 - Tiotidine

Figure 5 – Intermediate Compound

Figure 5* ----Intermediate Compound

The district court correctly rejected Danbury's argument. Specifically, Danbury did not show sufficient motivation for one of ordinary skill in the art at the time of invention to take any one of the following steps, let alone the entire complex combination: (1) selecting example 44 as a lead compound, (2) combining the polar tail *1345 from example 44 with the substituted heterocycle from tiotidine, and (3) substituting the carbamoyl (CONH2) group in the intermediate compound with a sulfamoyl group (SO2NH2) to create famotidine.

At the outset, Danbury did not show the required motivation for selecting example 44 as a lead compound. Danbury's assertion of motivation rests on the fact that example 44 is three times more active than cimetidine. That activity alone, however, is not sufficient motivation. As the trial court noted, other prior art references disclosed

compounds with H2 antagonist activity up to ten times higher than cimetidine. See Yamanouchi, 21 F.Supp.2d at 373. If activity alone was the sole motivation, other more active compounds would have been the obvious choices, not example 44.

Danbury also does not show the motivation to combine the polar tail of example 44 with the substituted heterocycle of tiotidine, then to substitute the carbamoyl with a sulfamoyl. To show such motivation, Danbury argues only that an ordinary medicinal chemist would have reasonably expected the resulting compound to exhibit the baseline level of H2 antagonist activity. The baseline level of activity is a mere 1/165 th the activity of cimetidine. This level of motivation does not show a "reasonable expectation of success." " In re Longi, 759 F.2d at 897. The success of discovering famotidine was not discovering one of the tens of thousands of compounds that exhibit baseline H2 antagonist activity. Rather, the success was finding a compound that had high activity, few side effects, and lacked toxicity. As Danbury's expert testified, the ordinary medicinal chemist

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would not have expected famotidine to have the " most desirable combination of pharmacological properties" that it possesses. J.A. at 1052.

Furthermore, the prior art offers no suggestion to pursue the particular order of manipulating parts of the compounds. Danbury's proposed obvious course of invention requires a very specific series of steps. Any deviation in the order of combination would have taught away from famotidine. If, for instance, the sulfamoyl group were substituted for the carbamoyl group on example 44 without attaching the substituted heterocycle from tiotidine, the evidence showed that the resulting compound would have 1/100 th the activity of cimetidine. Famotidine, on the other hand, has 40 times the activity of cimetidine. Danbury offered no evidence suggesting what might have led an ordinary artisan in this field to follow the precise steps that produced a remarkable invention.

Danbury falls far short of satisfying its burden of showing a prima facie case for structural obviousness by clear and convincing evidence. Instead, as the district court aptly concluded, this case "has all the earmarks of somebody looking at this from hindsight." Yamanouchi, 21 F.Supp.2d at 370. Because Danbury did not show even a prima facie case for obviousness, this court has considered, but need not separately address, the strong objective evidence of non-obviousness.

B.

[5] On appeal, Danbury contends that the district court improperly rejected its request to examine the inventor of the '408 patent, Dr. Yanagisawa, and thereby abridged its right to be fully heard. At trial, Danbury proffered that Dr. Yanagisawa's testimony would show an alleged distortion in his data provided to the U.S. Patent and Trademark Office. The alleged distortion, according to Danbury, would prove that tiotidine is actually more active than famotidine.

Upon review, this court concludes that the district court did not abuse its discretion in excluding Dr. Yanagisawa as a witness. Under Rule 52(c), "the

right to be 'fully heard' does not amount to a right to introduce every shred of evidence that a party wishes, without regard to the probative value of that evidence." First Va. Banks, Inc. v. BP Exploration & Oil, Inc., 206 F.3d 404, 407 (4th Cir.2000); see *1346Granite State Ins. Co. v. Smart Modular Tech., Inc., 76 F.3d 1023, 1031 (9th Cir.1996). Moreover, the advisory committee notes clarify that the rule "authorizes the court to enter judgment at any time that it can appropriately make a dispositive finding of fact on the evidence." Fed.R.Civ.P. 52 advisory committee notes (1991 amendment).

In the present case, the district court made a dispositive finding that the record showed no motivation to combine the prior art in the way suggested by Danbury. Dr. Yanagisawa's testimony would not bear on this dispositive finding. Rather, Danbury's own expert, Dr. Loev, testified that famotidine is more active than tiotidine-a position directly contrary to what Danbury stated would be shown by Dr. Yanagisawa's testimony. Further, Danbury, on appeal, admitted that it had an opportunity to notice and depose Dr. Yanagisawa, but did not do so.

Accordingly, this court agrees with the district court's finding that Danbury was fully heard within the meaning of Rule 52(c). This court therefore affirms the district court's grant of JMOL, sustaining the validity of claim 4 of the '408 patent.

III.

[6] This court reviews the district court's decision to award attorney fees under an abuse of discretion standard. See Avia Group Int'l., Inc. v. L.A. Gear Cal., Inc., 853 F.2d 1557, 1567, 7 USPQ2d 1548, 1556 (Fed.Cir.1988). Under that standard, this court affirms the district court's decision unless the court's decision is clearly unreasonable, arbitrary or fanciful, or based on an erroneous conclusion of law or fact. See Heat & Control, Inc. v. Hester Indus., Inc., 785 F.2d 1017, 1022, 228 USPQ 926, 930 (Fed.Cir.1986) (citations omitted).

[7] At the outset, this court recognizes that the Hatch-Waxman Act authorizes an award of attorney

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fees to the prevailing party in exceptional cases on the basis of an ANDA filing. As an initial matter, title 35 recognizes that the submission of an ANDA "shall be an act of infringement ... if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug ... claimed in a patent ... before the expiration of such patent." 35 U.S.C. § 271(e)(2) (emphasis added). Thus, under the terms of the Act, an ANDA filer may infringe without even engaging in any actual commercial activities. The mere act of filing an ANDA constitutes infringement.

The Act also permits an award of attorney fees for infringement by an ANDA filing. Section 271(e)(4) states: "For an act of infringement described in paragraph (2) ... a court may award attorney fees under section 285." Section 285, in turn, provides: "The court in exceptional cases may award reasonable attorney fees to the prevailing party." U.S.C. § 285. The "paragraph infringement specified in § 271(e)(4) is the filing of an ANDA. Accordingly, the Act unambiguously permits an award of attorney fees to the prevailing party in exceptional cases on the basis of an ANDA filing.

In fact, the Act singles out paragraph (2) infringement - ANDA filings - as a basis for an attorney fee award. In the same section, the Act allows damages and other monetary relief "only if there has been commercial manufacture, use, offer to sell, or sale within the United States ... of an approved drug." 35 U.S.C. § 271(e)(4)(C). Yet with regard to paragraph (2) infringement, the Act incorporates no such restriction, but rather authorizes fee awards. Accordingly, the Act itself does not limit an award of attorney fees for paragraph (2) infringement to cases involving infringing commercial sales. See 35 U.S.C. § 271(e)(4).

As noted above, section 271(e)(4) authorizes fee awards for paragraph (2) infringement in accordance with the standards for section 285 exceptional cases. This court, in turn, has recognized many varieties of misconduct that make a case exceptional for a fee award. These forms *1347 of misconduct include willful infringement, see, e.g., Avia, 853 F.2d at 1567; Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1548, 221 USPQ 1, 8-9 (Fed.Cir.1984), inequitable conduct before the PTO, offensive litigation tactics, vexatious or unjustified litigation, or frivolous filings, see Hoffmann-La Roche Inc. v. Invamed Inc., 213 F.3d 1359, 1365, 54 USPQ2d 1846, 1850 (Fed.Cir.2000); Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed.Cir.1989).

[8] In the present case, the district court determined that Danbury's conduct amounted to willful infringement. See Yamanouchi, 21 F.Supp.2d at 376. An ANDA filing by its very nature is a " highly artificial act of infringement," therefore, the trial court need not have elevated the ANDA certification into a finding of willful infringement. See Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 678, 110 S.Ct. 2683, 110 L.Ed.2d 605, 15 USPQ2d 1121, 1130 (1990). Rather, Danbury's misconduct in filing a wholly unjustified ANDA certification and misconduct during the litigation that followed warranted the district court's finding that this case was exceptional.

The joint operation of §§ 271(e) and 285 require the paragraph (2) infringer to display care and regard for the strict standards of the Hatch-Waxman Act when challenging patent validity. As already the Hatch-Waxman Act challenges to the validity of patents in accordance with strict statutory requirements. Specifically, a paragraph IV filing requires "a certification, in the opinion of the applicant and to the best of his knowledge, [that] each patent ... for which the applicant is seeking approval ... is invalid." 21 U.S.C. \S 355(j)(2)(A)(vii)(IV) (emphasis added). The Hatch-Waxman Act thus imposes a duty of care on an ANDA certifier. Thus, a case initiated by a paragraph (2) filing, like any other form of infringement litigation, may become exceptional if the ANDA filer makes baseless certifications.

This court concludes that the district court's finding that Danbury made a baseless certification is not clearly erroneous. In the first place, Danbury's case for obviousness presented at trial contained glaring

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weaknesses, precipitating a JMOL. The ANDA certification notice and its supporting affidavits, upon which Danbury relies to show that it had a good faith belief in invalidity, suffer similar weaknesses. The certification statute requires notice to the patentee of "the factual and legal basis" of invalidity. See 21 U.S.C. § 355(j)(2)(B)(ii). Danbury's notice does not present a prima facie case of invalidity, and makes no reference to famotidine's potency, safety, and lack of side effects, among other distinguishing properties accompanying its unusually high activity. See Yamanouchi, 21 F.Supp.2d at 376. "Moreover, Dr. Loev admitted at trial that, as of 1992, he could not tell from [famotidine's] chemical structure whether it would be toxic nor predict its lack of side effects. He further testified that he could not predict the effects on potency that would be caused by the structural manipulations he claimed to be obvious." Id. When Danbury proceeded in the face of these weaknesses, its certification amounted to baseless unjustified misconduct. In certifying invalidity, Danbury disregarded its duty to exercise due care.

In assessing whether a case qualifies as exceptional, the district court must look at the totality of the circumstances. See Kaufman Co., Inc. v. Lantech, Inc., 807 F.2d 970 at 978-79, 1 USPQ2d 1202, 1208 (Fed.Cir.1986). These circumstances include Danbury's choice to produce during trial a 1993 opinion from its patent attorney, Mr. Alfred B. Engelberg. This legal opinion contained an acknowledged error in chemistry, which was critical to its conclusion of obviousness. Danbury's own expert, Dr. Loev, conceded at trial that "Engelberg's interpretation of the ['408] patent was patently incorrect and that the ['408] patent nowhere described the formulation relied upon by Engelberg. " See Yamanouchi, 21 F.Supp.2d at 376.

*1348 Based on the foregoing, the district court properly found that Danbury's ANDA filing was " without adequate foundation and speculative at best. " Yamanouchi, 21 F.Supp.2d at 376. The district court thus found the case "exceptional" and awarded attorney fees to Yamanouchi. This court detects no abuse of discretion by the district court in its award. This court therefore affirms the district court's award of attorney fees to Yamanouchi.

CONCLUSION

Because the prior art does not render obvious claim 4 of the '408 patent, this court affirms the district court's grant of JMOL upholding its validity. Moreover, because the district court did not abuse its discretion in awarding attorney fees, this court affirms.

COSTS

Each party shall bear its own costs.

AFFIRMED.

C.A.Fed. (N.Y.),2000.

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Briefs and Other Related Documents (Back to top)

- 2000 WL 34467099 (Appellate Petition, Motion and Filing) Appellants' Combined Petition for Panel Rehearing and Rehearing En Banc (Nov. 17, 2000) Original Image of this Document with Appendix (PDF)
- 2000 WL 34004081 (Appellate Brief) Appellants' Reply Brief (Feb. 09, 2000) Original Image of this Document (PDF)
- 2000 WL 34004083 (Appellate Brief) Brief for Plaintiffs-Appellees (Jan. 12, 2000) Original Image of this Document (PDF)
- 1999 WL 33631183 (Appellate Brief) Brief for Amicus Curiae National Pharmaceutical Alliance in Support of Defendants-Appellants (Dec. 01, 1999) Original Image of this Document (PDF)
- 1999 WL 33631182 (Appellate Brief) Appellants' Brief (Nov. 01, 1999) Original Image of this Document with Appendix (PDF)
- 99-1521 (Docket) (Jul. 26, 1999)

END OF DOCUMENT

Westlaw.

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C

United States Court of Appeals, Federal Circuit. In re Peter S. MILLS. No. 90-1184.

Oct. 9, 1990.

Applicant appealed from order of the Board of Patent Appeals and Interferences which rejected claims. The Court of Appeals, Lourie, Circuit Judge, held that fact that referenced prior art might be capable of being modified to run the way claimed by applicant for his apparatus did not render his apparatus obvious.

Reversed.

West Headnotes

[1] Patents 291 \$\infty\$45

291 Patents

291II Patentability 291II(B) Novelty

291k45 k. Evidence of Novelty. Most

Cited Cases

Determination of Board of Patent Appeals and Interferences that differences between the claim and machine described in prior art lay solely in the functional language of the claim suggested lack of novelty rather than obviousness. 35 U.S.C.A. §§ 102, 103.

[2] Patents 291 5 314(5)

291 Patents

291XII Infringement 291XII(C) Suits in Equity

291k314 Hearing

291k314(5) k. Questions of Law or

Fact. Most Cited Cases

Nonobviousness is a question of law to be determined from the facts. 35 U.S.C.A. § 103.

[3] Patents 291 \$\infty\$113(6)

291 Patents

291IV Applications and Proceedings Thereon of 291k113 Appeals from Decisions Commissioner of Patents

291k113(6) k. Review on Appeal in General. Most Cited Cases

Board of Patent Appeals and Interferences' determination of obviousness is reviewed for correctness or error. 35 U.S.C.A. § 103.

[4] Patents 291 € 16.24

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.24 k. Building Materials and Methods. Most Cited Cases

Claim for apparatus for mixing cementitious material involving a pump means and feed means with a pumping capacity greater than the feed rate of the ingredients into the mixing chamber in order to draw air into the mixing chamber and entrain it in the mixed ingredients was not obvious in light of prior patent for mixing cementitious material through a device in which the pumping speed could be greater than the feed speed, as the prior device made no reference to producing area rated cementitious material. 35 U.S.C.A. § 103.

[5] Patents 291 \$\infty\$16(2)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16 Invention and Obviousness in General

291k16(2) k. Prior Art in General.

Most Cited Cases

Fact that prior art apparatus may be capable of being modified to run the way claimed by another's apparatus does not render the new apparatus obvious if there is no suggestion or motivation in

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the reference to do so. 35 U.S.C.A. § 103.

[6] Patents 291 5 16(2)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16 Invention and Obviousness in

General

291k16(2) k. Prior Art in General.

Most Cited Cases

On the issue of obviousness, it is not pertinent whether prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure. 35 U.S.C.A. § 103.

Patents 291 5 328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most Cited

2,717,770, 4,117,547. Cited.

*680 James C. Wray, McLean, Va., argued for appellant.

Muriel E. Crawford, Asst. Sol., Office of the Sol., Arlington, Va., argued for appellee. With her on the brief was Fred E. McKelvey, Sol.

Before MAYER and LOURIE, Circuit Judges, and MILLER, Senior Circuit Judge.

*681 LOURIE, Circuit Judge.

This appeal is from the November 2, 1989, decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (Board), Appeal No. 88-0141, affirming the examiner's rejection, under 35 U.S.C. § 103, of claims 6-9 and 11-14 in Mills' application Serial No. 891,374, a continuation of Serial No. 607-805, filed May 4, 1984, entitled "Methods of and Apparatus for Producing Aerated Cementitious Compounds." The remainder of the claims (1-5, 10, and 15) have all been cancelled. We reverse.

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I

BACKGROUND

A. The Invention

Mills' claimed invention is an apparatus for producing aerated cemetitious compositions. Claim 6 is the broadest claim:

6. Apparatus for producing an aerated cementitious composition, comprising

a mixing chamber being open to atmosphere and containing mixing means,

feed means for feeding ingredients comprising cement, foaming agent and liquid to the mixing chamber,

mixing means for mixing ingredients fed to the mixing chamber, pump means for pumping the mixed ingredients to a desired site and having a pump inlet connected to an outlet of the mixing chamber.

drive motor means connected through gearbox means providing a pumping capacity of the pump means greater than the feed rate of the ingredients to the mixing chamber provided by the feed means, such that in operation air is drawn into the mixing chamber, and entrained in the mixed ingredients.

The essence of Mills' invention is the machine's ability to aerate a cementitious composition by driving the output pump at a capacity greater than the feed rate, thereby drawing air into This aeration produces composition. composition with substantially lower density than standard composition mixing cemetitious ingredients.

B. The Reference

The sole reference upon which the Board relied in affirming the examiner's rejection was Mathis et al. U.S. Patent 4,117,547 (Mathis). FN1 Mathis discloses a mixing chamber which is open to the atmosphere and which contains a mixing means. Two feed means for feeding ingredients in the

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mixing chamber are provided. The first feed means may consist of a screw conveyer and the second, a flow metering device such as an adjustable valve. A pump means pumps the mixture from the mixing chamber to a desired site and a drive motor means is connected to mixing means and pump means. A separate motor drives the feed means.

> FN1. The examiner rejected the claims at issue under 35 U.S.C. § 103 as being unpatentable not only over Mathis but also in view of Gibson et al. U.S. Patent 2,717,770. However, the Board affirmed the examiner's rejection of claims 6-9 and 11-14 based solely on the Mathis reference. With regard to Gibson the Board stated:

> We view the teachings of Gibson at best as being merely confirmatory of the fact that aerated mixtures can be produced by machines in which a pump means operates upon a mixing chamber at a greater rate than the ingredients are fed thereunto so that air is drawn into the mixing chamber and entrained in the mixed ingredients. App. 2.

A control system exists to arrest the feed means so as not to overfill the mixing chamber. This system comprises a level detector in the mixing chamber, which signals the feed means to close when the mixing chamber stores the predetermined maximum permissible quantity of material.

C. The Rejection

The Board affirmed the examiner's Section 103 rejection of claims 6-9 and 11-14, "finding correspondence in the Mathis reference for all of the subject matter recited in the appellants' claims.... " With regard to Mills' claim language relating to aerating the mixture, the Board stated: "[i]n our opinion, the differences between claim 6 and the Mathis machine ... lie solely in *682 the functional language of the claim." The Board further found that Mathis teaches the use of separate input and

output motors in order to permit the various mixing means and pumps to operate at different rates, and that Mathis "contemplates a situation wherein the rate of the outlet pump would be greater than the inlet pumps...." The Board concluded on this point: "[w]e are of the opinion that the Mathis machine is capable of being operated in such a fashion as to cause [the output] pump 18 to draw air into the mixing chamber 17 so that it is entrained in the mixture."

The Board also agreed with Mills' contention that Mathis is not directed to the problem of producing aerated cementitious material, but noted that Mills is not claiming a method, but an apparatus, and all of Mills' apparatus structure is present in the Mathis machine.

II

DISCUSSION

[1] All of the rejected claims are apparatus claims. The Board found "correspondence in the Mathis reference for all of the subject matter recited in appellants' claims" and that "[t]he Mathis machine discloses all of the structure set forth in claim 1" (a method claim not before us). It asserts that the use of such a mechanism would have been obvious and that the differences between claim 6 and the Mathis machine lie solely in the functional language of the claim, the preamble merely stating an intended use for the machine. This language suggests a lack of novelty rejection under 35 U.S.C. § 102, rather than an obviousness rejection. However, no Section 102 rejection has been made or is before us. What is before us is a rejection for obviousness, and we must decide whether the Board erred in that rejection.

[2] [3] We note first that nonobviousness is a question of law to be determined from the facts. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed.Cir.1983). We review the Board's determination of obviousness, based on the scope and content of the Mathis reference and the differences between the Mathis

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reference and the Mills claims, for correctness or error. In re Carleton, 599 F.2d 1021, 1024 n. 14, 202 USPQ 165, 169 n. 14 (CCPA 1979).

[4] [5] After reviewing the record, the arguments in the briefs, and the Mathis reference, we conclude that Mathis would not have rendered the claimed invention obvious. The closest Mathis comes to suggesting Mills' claimed apparatus is at column 3, lines 42-47, which states

[T]he rate at which the inlet 2b receives a solid constituent depends on the speed of the feed screw 4. Such speed can be regulated by a prime mover 6 which includes a variable-speed transmission.

This brief reference contains no suggestion of " pump means and the feed means providing a pumping capacity of the pump means greater than the feed rate of ingredients to the mixing chamber provided by the feed means, such that in operation air is drawn into the mixing chamber, and air entrained in the mixed ingredients," as provided for in Mills' claim 6. While Mathis' apparatus may be capable of being modified to run the way Mills' apparatus is claimed, there must be a suggestion or motivation in the reference to do so. See In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed.Cir.1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."). We see no such suggestion. The apparatus claimed by Mills is different from that of Mathis, since the fact that motor 6 of Mathis (the feed means) can be run at a variable speed does not require that motor 20 (connected to the pump) be run at a lesser speed " such that in operation air is drawn into the mixing chamber and air entrained in the mixed ingredients."

[6] The Board found that the difference between the claimed subject matter and the prior art resided solely in functional language and that appellant had to show that the prior art device lacked the functional characteristics of the claimed device, citing *683 In re Ludtke, 441 F.2d 660, 58 C.C.P.A. 1159, 169 USPQ 563 (CCPA 1971). Ludtke, however, dealt with a rejection for lack of novelty, in which case it was proper to require that a prior art reference cited as anticipating a claimed

invention be shown to lack the characteristics of the claimed invention. That proof would in fact negate the assertion that the claimed invention was described in the prior art. We are here, however, facing an obviousness issue. It is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure. That is the case here. Given the facts before us, we hold that the Board was in error in affirming the examiner's rejection of claims 6-9 and 11-13 as obvious in view of Mathis, and we therefore reverse the Board.

REVERSED.

C.A.Fed.,1990. In re Mills 916 F.2d 680, 16 U.S.P.Q.2d 1430, 59 USLW 2259

END OF DOCUMENT

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Westlaw.

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Briefs and Other Related Documents

United States Court of Appeals, Federal Circuit. AL-SITE CORPORATION and Magnivision, Inc., Plaintiffs-Appellants,

VSI INTERNATIONAL, INC. and Myron Orlinsky, Defendants-Cross Appellants. Nos. 97-1593, 98-1008.

March 30, 1999.

Rehearing and Suggestion for Rehearing En Banc Denied May 25, 1999.

Assignee of patents claiming hangers for displaying non-prescription eyeglasses brought action against competitor and competitor's chairman, alleging patent, trademark, and trade dress infringement. After granting assignee's motion for summary judgment on competitor's defense of inequitable conduct, 1997 WL 579201, and then conducting jury trial, the United States District Court for the Southern District of Florida, C. Clyde Atkins, Senior Judge, entered judgment upon jury verdict finding literal infringement of one patent, infringement of remaining patents under doctrine of trademark and trade equivalents, infringement, and unfair competition. The jury also personal liability on competitor's imposed chairman, making him jointly and severally liable for the damage award. Parties appealed. The Court of Appeals, Rader, Circuit Judge, held that: (1) one patent was literally infringed; (2) remaining patents were also infringed; (3) patents were not invalid for obviousness; (4) competitor did not infringe trade dress of assignee's display cards, color coding system, or eyeglass colors and styles; (5) competitor did not infringe assignee's "MAGNIVISION" trademark; (6) competitor did not engage in unfair competition; and (7) chairman was not personally liable for patent infringement.

Affirmed in part and reversed in part.

West Headnotes

[1] Federal Courts 170B € 765

170B Federal Courts

170BVIII Courts of Appeals

170BVIII(K) Scope, Standards, and Extent

170BVIII(K)1 In General

170Bk763 Extent of Review

Dependent on Nature of Decision Appealed from

k. Judgment 170Bk765

Notwithstanding Verdict. Most Cited Cases

Court of Appeals reviews the district court's denials of motions for judgment as a matter of law using the same standards applied by the district court and will only upset a jury verdict if the record lacks substantial evidence to support the verdict.

[2] Patents 291 237

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement

291k233 Patents for Machines

Manufactures

291k237 k. Substitution of Equivalents.

Most Cited Cases

Patent for hanger used to display eyeglasses, which described use of rivet or button as fastening means, was literally infringed by accused hanger which used adhesive fastening means, because adhesive was equivalent to structure disclosed in patent specification, and adhesive was "in engagement" with extension that projected from bottom edge of hanger body, as required by the patent.

[3] Federal Courts 170B 5 844

170B Federal Courts

170BVIII Courts of Appeals

170BVIII(K) Scope, Standards, and Extent 170BVIII(K)5 Questions of Fact, Verdicts

and Findings

170Bk844 k. Credibility of Witnesses

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in General. Most Cited Cases As the finder of fact, the jury receives deference for its function of weighing witness demeanor, credibility, and meaning.

[4] Patents 291 \$\iiii 314(5)\$

291 Patents 291XII Infringement 291XII(C) Suits in Equity 291k314 Hearing 291k314(5) k. Questions of Law or Fact. Most Cited Cases Court of Appeals reviews the district court's patent claim interpretation without deference.

[5] Patents 291 \$\infty\$ 101(8)

291 Patents

291IV Applications and Proceedings Thereon 291k101 Claims

291k101(8) k. Functions, Advantages or Results of Invention. Most Cited Cases If the word "means" appears in a patent claim element in combination with a function, it is presumed to be a means-plus-function element under patent statute, although, according to its express terms, means-plus-function provision governs only claim elements that do not recite sufficient structural limitations, and presumption that means-plus-function provision applies is overcome if the claim itself recites sufficient structure or material for performing the claimed function. 35 U.S.C.A. § 112.

[6] Patents 291 \$\infty\$101(8)

291 Patents

291IV Applications and Proceedings Thereon 291k101 Claims

291k101(8) k. Functions, Advantages or Results of Invention. Most Cited Cases Although use of the phrase "means for" or "step for" is not the only way to invoke statutory means-plus-function provision, that terminology typically invokes the provision while other formulations generally do not; therefore, when an element of a claim does not use the term "means," treatment as a means-plus-function claim element is

generally not appropriate. 35 U.S.C.A. § 112.

[7] Patents 291 \$\infty\$ 101(8)

291 Patents

291IV Applications and Proceedings Thereon 291k101 Claims

291k101(8) k. Functions, Advantages or Results of Invention. Most Cited Cases When it is apparent that an element of a patent claim invokes purely functional terms, without the additional recital of specific structure or material for performing that function, the claim element may be a means-plus-function element despite the lack of express means-plus-function language. 35 U.S.C.A. § 112.

[8] Patents 291 \$\infty\$ 226.7

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement 291k226.5 Substantial Identity of Subject

Matter

291k226.7 k. Function, Operation, and Result. Most Cited Cases Term "eyeglass hanger member" in patents for hangers used to display eyeglasses did not trigger application of statutory means-plus-function provision, as elements were not in traditional means-plus-function format, and claims themselves contained sufficient structural limitations for performing specified function of mounting a pair of eyeglasses. 35 U.S.C.A. § 112.

[9] Patents 291 \$\infty\$ 226.7

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement 291k226.5 Substantial Identity of Subject

Matter

291k226.7 k. Function, Means, Operation, and Result. Most Cited Cases Element of patent claim described as "attaching portion attachable to a portion of said frame of said pair of eyeglasses," in patent for hanger used to display eyeglasses, did not trigger application of statutory means-plus-function provision, as claim

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element was not in traditional means-plus-function form and supplied structural, not functional, terms. 35 U.S.C.A. § 112.

[10] Patents 291 226.7

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement 291k226.5 Substantial Identity of Subject

Matter

291k226.7 k. Function, Means,

Operation, and Result. Most Cited Cases

Term "eyeglass contacting member" in patent for hangers used to display eyeglasses did not trigger means-plus-function application of statutory provision, as elements were not in traditional means-plus-function format, and claim recited sufficient structure for performing recited function. 35 U.S.C.A. § 112.

[11] Patents 291 \$\infty\$237

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement Patents for Machines 291k233 or

Manufactures

291k237 k. Substitution of Equivalents.

Most Cited Cases

Jury's finding that structure of accused eyeglass hanger was equivalent to "means for securing" element of claimed eyeglass hanger under the doctrine of equivalents supported inference that jury considered accused structure to be "equivalent" of claimed hanger, for purpose of determining literal infringement under means-plus-function analysis, so any error in district court's claim construction and resulting instruction that led to finding of infringement under doctrine of equivalents, rather than finding of literal infringement, was harmless.

[12] Patents 291 \$\infty\$ 237

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement Machines 291k233 Patents for

or

Manufactures

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291k237 k. Substitution of Equivalents.

Most Cited Cases

statute's "equivalent" under patent means-plus-function provision informs the claim meaning for a literal infringement analysis, by restricting the scope of a functional claim limitation, while the "doctrine of equivalents" extends enforcement of claim terms beyond their literal reach in the event there is equivalence between the elements of the accused product or process and the claimed elements of the patented invention. 35 U.S.C.A. § 112.

[13] Patents 291 \$\iiint 237

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement 291k233 Patents for Machines Manufactures

291k237 k. Substitution of Equivalents.

Most Cited Cases

An equivalent structure or act under patent statute's means-plus-function provision cannot embrace technology developed after the issuance of the patent because the literal meaning of a claim is fixed upon its issuance; an "after arising equivalent" infringes, if at all, under the doctrine of equivalents, and an after-arising technology could infringe under the doctrine of equivalents without infringing literally as a mean-plus-function equivalent. 35 U.S.C.A. § 112.

[14] Patents 291 \$\infty\$237

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement 291k233 Patents for Machines Manufactures

291k237 k. Substitution of Equivalents.

Most Cited Cases

patent means-plus-function Under statute's provision, an accused device must perform the identical function as recited in the claim element, while the doctrine of equivalents may be satisfied when the function performed by the accused device is only substantially the same. 35 U.S.C.A. § 112.

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[15] Patents 291 € 237

291 Patents

291XII Infringement

291XII(A) What Constitutes Infringement 291k233 Patents for Machines or Manufactures

291k237 k. Substitution of Equivalents.

Most Cited Cases

Where there is identity of function and no after-arising technology, a means-plus-function element of a patent claim that is found to be infringed only under the doctrine of equivalents due to a jury instruction failing to instruct on structural equivalents for means-plus-function purposes is also literally present in the accused device. 35 U.S.C.A. § 112.

[16] Patents 291 \$\infty\$169

291 Patents

291IX Construction and Operation of Letters Patent

291IX(B) Limitation of Claims

291k169 k. Litigation Affecting Patent.

Most Cited Cases

District court's construction of "opening means" element in patent for eyeglass hanger to mean the elongated slot having a notch as described and depicted in the patent, and the structural equivalents thereof, was not barred by prior Court of Appeals opinion construing separate patent assigned to same patentee; claims had different language and different meanings, Court of Appeals opinion was nonprecedential, and record did not indicate that Court had rejected construction at issue or that alleged infringer should be denied the opportunity to seek a narrower construction.

[17] Patents 291 \$\infty\$ 168(2.1)

291 Patents

291IX Construction and Operation of Letters Patent

291IX(B) Limitation of Claims

291k168 Proceedings in Patent Office in

General

291k168(2) Rejection and Amendment

of Claims

291k168(2.1) k. In General. Most

Cited Cases

Prosecution history related to one patent did not give rise to estoppel in connection with later patents that arose from related applications, where specific limitation added in claims of earlier issued patent was not present in claims of later issued patents.

[18] Patents 291 5 314(5)

291 Patents

291XII Infringement

291XII(C) Suits in Equity

291k314 Hearing

291k314(5) k. Questions of Law or

Fact. Most Cited Cases

Although the determination of whether a patent is obvious is ultimately a legal conclusion, it rests on underlying factual determinations. 35 U.S.C.A. § 103.

[19] Patents 291 \$\iiins 312(1.2)\$

291 Patents

291XII Infringement

291XII(C) Suits in Equity

291k312 Evidence

291k312(1) Presumptions and Burden

of Proof

291k312(1.2) k. Patentability and

Validity. Most Cited Cases

Issued patents have a strong presumption of validity in infringement proceedings, and, hence, an accused infringer who defends on grounds of patent invalidity bears the burden of showing patent invalidity by clear and convincing evidence. 35 U.S.C.A. § 282.

[20] Patents 291 \$\infty\$16.5(1)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.5 State of Prior Art and

Advancement Therein

291k16.5(1) k. In General. Most Cited

Cases

Patents 291 € 36(2)

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291 Patents

291II Patentability

291II(A) Invention; Obviousness 291k36 Weight and Sufficiency

291k36(2) k. Degree of Proof and

Doubt as to Invention. Most Cited Cases

In a challenge to a patent based on obviousness, the person alleging invalidity must show prior art references which alone or combined with other references would have rendered the invention obvious to one of ordinary skill in the art at the time of invention, and, because the presumption of validity carries with it a presumption that the patent examiner did his duty and knew what claims he was allowing, the challenger's burden is especially difficult when the prior art was before the examiner during prosecution of the application. 35 U.S.C.A. §§ 103, 282.

[21] Patents 291 \$\infty\$16(2)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16 Invention and Obviousness in General

291k16(2) k. Prior Art in General.

Most Cited Cases

Party seeking patent invalidity based obviousness must show some motivation or suggestion to combine the prior art teachings, which generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. 35 U.S.C.A. § 103.

[22] Patents 291 \$\infty\$ 16.18

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.18 k. Structure and Appearance.

Most Cited Cases

Patents for hangers used to display non-prescription eyeglasses were not invalid for obviousness, as there was no evidence of specific teaching or suggestion for combining prior art in such manner as to result in hanger with all elements of claimed hangers, evidence supported finding that one of

ordinary skill in the art would not have known to combination, secondary and make such supported considerations finding nonobviousness. 35 U.S.C.A. § 103.

[23] Patents 291 \$\infty\$16(3)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16 Invention and Obviousness in

General

291k16(3) k. View of Person Skilled in

Art. Most Cited Cases

The level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention, for purpose of claim that patent is obvious; this reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness. 35 U.S.C.A. § 103.

[24] Courts 106 \$\infty\$ 96(7)

106 Courts

106II Establishment, Organization, and Procedure

106II(G) Rules of Decision

106k88 Previous Decisions as Controlling or as Precedents

106k96 Decisions of United States Courts as Authority in Other United States Courts

106k96(7) k. Particular Questions

or Subject Matter. Most Cited Cases

For areas of law, such as trademark and trade dress infringement, which are not unique to jurisdiction of the Court of Appeals for the Federal Circuit, that Court applies the law of the pertinent regional circuit.

[25] Federal Courts 170B 5755

170B Federal Courts

170BVIII Courts of Appeals

170BVIII(K) Scope, Standards, and Extent

170BVIII(K)1 In General

170Bk754 Review Dependent on

Whether Questions Are of Law or of Fact

170Bk755 k. Particular Cases. Most

Cited Cases

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(Formerly 382k725)

Trademarks 382T € 1684

382T Trademarks 382TIX Actions and Proceedings 382TIX(E) Trial and Judgment 382Tk1682 Questions of Law or Fact 382Tk1684 k. Infringement in General.

Most Cited Cases (Formerly 382k704)

Trademarks 382T €=1693

382T Trademarks 382TIX Actions and Proceedings 382TIX(E) Trial and Judgment 382Tk1682 Questions of Law or Fact 382Tk1693 k. Trade Dress. Most Cited

Cases

(Formerly 382k704)

A finding of trademark and trade dress infringement is a question of fact, so a jury verdict of trademark or trade dress infringement is therefore reviewed for substantial evidence, although legal determinations of the district court receive no deference on review.

[26] Trademarks 382T € 1062

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1062 k. In General. Most Cited

Cases

(Formerly 382k43)

Trade dress protection embraces the total image of the product including such factors as the size, shape, and color of the product's packaging and appearance.

[27] Trademarks 382T 2 1436

382T Trademarks 382TVIII Violations of Rights 382TVIII(A) In General 382Tk1436 k. Trade Dress. Most Cited Cases (Formerly 382k349, 382k43)

To prove trade dress infringement, the plaintiff must show: (1) the inherent distinctiveness or secondary meaning of its trade dress, (2) the essential nonfunctionality of its trade dress, and (3) the likelihood of consumer confusion as to origin, sponsorship, or approval due to similarity between its and the defendant's trade dress.

[28] Trademarks 382T € 1063

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1063 k. Distinctiveness; Secondary

Meaning. Most Cited Cases

(Formerly 382k43)

"Distinctive" trade dress enables consumers to distinguish a product from others and identify that product with its source.

[29] Trademarks 382T \$\infty\$=1063

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1063 k. Distinctiveness; Secondary

Meaning. Most Cited Cases

(Formerly 382k43)

Distinctiveness of trade dress is based on whether it is a common basic shape or design, whether it is unique or unusual in a particular field, and whether it is a mere refinement of a commonly adopted and well-known form of ornamentation for a particular class of goods viewed by the public as a dress or ornamentation for the goods.

[30] Trademarks 382T € 1063

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1063 k. Distinctiveness; Secondary

Meaning. Most Cited Cases

(Formerly 382k43)

Trade dress can satisfy distinctiveness requirement by showing "secondary meaning," or a connection

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in the consumer's mind between the mark and the product's producer, whether that producer is known or unknown.

[31] Trademarks 382T € 1063

382T Trademarks 382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1063 k. Distinctiveness; Secondary Meaning, Most Cited Cases (Formerly 382k43)

Trademarks 382T €=1631

382T Trademarks 382TIX Actions and Proceedings 382TIX(C) Evidence

382Tk1620 Weight and Sufficiency 382Tk1631 k. Trade Dress. Most Cited

Cases

(Formerly 382k43)

Plaintiff may show secondary meaning of trade dress with consumer surveys and with evidence of lengthy and uniform display of the dress or with evidence of the plaintiff's efforts, usually through advertising, to establish in the minds of the consumers a connection between the trade dress and its product; the plaintiff may also use other evidence showing consumers' association of the trade dress with the plaintiff or its product to prove secondary meaning.

[32] Trademarks 382T 5 1064

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1064 k. Functionality. Most Cited

(Formerly 382k43)

A trade dress is "functional" if it is essential to the use or purpose of the article or if it affects the cost or quality of the article, such that its protection would place a competitor at a significant disadvantage.

[33] Trademarks 382T = 1118

382T Trademarks

382TIII Similarity Between Marks; Likelihood of Confusion

382Tk1117 Trade Dress

382Tk1118 k. In General. Most Cited

Cases

(Formerly 382k349)

Determining whether a likelihood of confusion exists as result of alleged trade dress infringement requires weighing several factors: (1) the nature of the plaintiff's mark, (2) the similarity of the marks, (3) the similarity of the products the marks represent, (4) the similarity of the parties' retail outlets and customers, (5) the similarity of the parties' advertising, (6) the defendant's intent to copy or imitate the plaintiff's mark, and (7) the extent of actual confusion.

[34] Trademarks 382T € 1065(2)

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

> 382Tk1065 Particular Cases or Products 382Tk1065(2) k. Distinctiveness;

Secondary Meaning. Most Cited Cases (Formerly 382k43)

Trademarks 382T €== 1436

382T Trademarks

382TVIII Violations of Rights 382TVIII(A) In General

382Tk1436 k. Trade Dress. Most Cited

Cases

(Formerly 382k43)

Trade dress of plaintiff's display card and blister pack used to market hand-held magnifiers was not to protection absent evidence distinctiveness or secondary meaning or evidence to show likelihood of consumer confusion, regardless of whether plaintiff was sole user of its design.

[35] Trademarks 382T € 1063

382T Trademarks

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382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1063 k. Distinctiveness; Secondary Meaning. Most Cited Cases

(Formerly 382k478)

Sole use of a design is a preliminary step for a descriptive trade dress to acquire distinctiveness and secondary meaning.

[36] Trademarks 382T \$\infty\$ 1065(2)

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1065 Particular Cases or Products 382Tk1065(2) k. Distinctiveness: Secondary Meaning. Most Cited Cases

(Formerly 382k43)

Trademarks 382T € 1065(3)

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1065 Particular Cases or Products 382Tk1065(3) k. Functionality. Most

Cited Cases

(Formerly 382k43)

Color coding system used by maker of display hangers for nonprescription eyeglasses, by which eyeglasses of particular power would feature same color of stripe on hanger tag, was not entitled to trade dress protection, as there was no evidence of distinctiveness or secondary meaning, and system was primarily functional.

[37] Trademarks 382T €=1063

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1063 k. Distinctiveness; Secondary Meaning. Most Cited Cases (Formerly 382k43)

Color itself is not inherently distinctive, for purpose

of trade dress protection.

[38] Trademarks 382T \$\infty\$=1062

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

382Tk1062 k. In General. Most Cited

Cases

(Formerly 382k43)

Absent a specifically defined, color-definite, and stable visual appearance, an alleged trade dress cannot receive protection.

[39] Trademarks 382T \$\infty\$ 1065(2)

382T Trademarks

382TII Marks Protected

382Tk1061 Form, Features, or Design of Product as Marks; Trade Dress

> 382Tk1065 Particular Cases or Products 382Tk1065(2) k. Distinctiveness;

Secondary Meaning. Most Cited Cases

(Formerly 382k43)

Colors and styles of six of manufacturer's eyeglasses were not entitled to trade dress protection, as there was no evidence that colors and styles were inherently distinctive or possessed secondary meaning, in view of their public availability, and manufacturer changed its styles to suit demand.

[40] Trademarks 382T \$\infty\$1421

382T Trademarks

382TVIII Violations of Rights

382TVIII(A) In General

382Tk1418 Practices Conduct

Prohibited in General; Elements

382Tk1421 k. Infringement. Most

Cited Cases

(Formerly 382k334.1)

To prove trademark infringement, a trademark owner must show a likelihood that consumers would confuse the defendant's mark with the protected mark.

[41] Trademarks 382T €==1081

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174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Cite as: 174 F.3d 1308)

382T Trademarks

382TIII Similarity Between Marks; Likelihood of Confusion

382Tk1081 k. Factors Considered in General. Most Cited Cases (Formerly 382k334.1)

Factors which contribute to a likelihood of confusion finding, in a trademark infringement action, include (1) the nature of the plaintiff's mark, (2) the similarity of the marks, (3) the similarity of the products represented by the marks, (4) the similarity of the retail outlets and consumers, (5) the nature and extent of the parties' advertising, (6) the defendant's intent to copy the plaintiff's mark, and (7) the extent of actual confusion; other relevant factors include the strength of the marks, the number and nature of similar marks in use on similar goods, the nature and extent of any actual confusion and the length of time during and conditions under which there has been concurrent use without evidence of actual confusion.

[42] Trademarks 382T € 1086

382T Trademarks

382TIII Similarity Between Marks; Likelihood of Confusion

382Tk1083 Nature of Confusion 382Tk1086 k. Actual Confusion. Most Cited Cases (Formerly 382k356)

Trademarks 382T €=1092

382T Trademarks

382TIII Similarity Between Marks; Likelihood of Confusion

382Tk1090 Nature of Marks 382Tk1092 k. Strength or Fame of Marks; Degree of Distinctiveness. Most Cited Cases (Formerly 382k356)

Trademarks 382T €== 1098

382T Trademarks

382TIII Similarity Between Marks; Likelihood of Confusion

382Tk1093 Relationship Between Marks 382Tk1098 k. Appearance, Sound, and Meaning. Most Cited Cases (Formerly 382k356)

Competitor's use of mark "MAGNA DOT" did not infringe assignee's "MAGNIVISION" trademark for nonprescription eyeglasses, as marks did not present a similar sound, meaning, or commercial there was evidence impression. MAGNA/MAGNI prefix and VISION suffix enjoyed wide use in the eyeglass industry on similar goods and services, and there was no evidence of actual confusion despite several years of simultaneous use in an identical market.

[43] Trademarks 382T € 1622

382T Trademarks 382TIX Actions and Proceedings 382TIX(C) Evidence 382Tk1620 Weight and Sufficiency 382Tk1622 k. Infringement in General. Most Cited Cases (Formerly 382k584.1)

Trademarks 382T €=1631

382T Trademarks 382TIX Actions and Proceedings 382TIX(C) Evidence 382Tk1620 Weight and Sufficiency 382Tk1631 k. Trade Dress. Most Cited

Cases

(Formerly 382k584.1)

Finding of unfair competition lacked substantial where only evidence of unfair evidence, competition came from claims of trademark and trade dress infringement, and, as matter of law, there was no trademark or trade dress infringement.

[44] Trademarks 382T € 1420

382T Trademarks 382TVIII Violations of Rights 382TVIII(A) In General 382Tk1418 **Practices** Conduct Prohibited in General; Elements 382Tk1420 k. Unfair Competition. Most Cited Cases (Formerly 382k461)

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Trademarks 382T €== 1436

382T Trademarks

382TVIII Violations of Rights 382TVIII(A) In General

382Tk1436 k. Trade Dress. Most Cited

Cases

(Formerly 382k461)

Unfair competition provides an additional degree of protection above that provided by trademark and trade dress law; although trademark and trade dress infringement may be the basis for a claim of unfair competition, it frequently requires the court to examine additional conduct that would not give rise to a claim of trademark infringement.

[45] Corporations 101 € 1.6(1)

101 Corporations

1011 Incorporation and Organization

101k1.6 Particular Occasions for **Determining Corporate Entity**

101k1.6(1) k. In General. Most Cited Cases

Corporations 101 € 1.7(2)

101 Corporations

101I Incorporation and Organization

101k1.7 Pleading and Procedure in **Determining Corporate Entity**

101k1.7(2) k. Evidence and Fact Questions. Most Cited Cases

Personal liability of officer for corporation's acts of patent infringement requires sufficient evidence to justify piercing the corporate veil; the corporate entity deserves respect and legal recognition unless specific, unusual circumstances justify disregarding the corporate structure. 35 U.S.C.A. § 271(a).

[46] Corporations 101 € 1.6(1)

101 Corporations

101I Incorporation and Organization

101k1.6 Particular Occasions **Determining Corporate Entity**

101k1.6(1) k. In General. Most Cited

Corporate officer's act of making sole decision to

continue using accused hanger tags corporation received cease and desist letters from patent assignee was not sufficient to impose personal liability on officer for patent infringement; officer acted within and according to strictures of corporate structure, record showed no instance of the corporation operating as officer's alter ego, and officer acted upon advice of counsel. 35 U.S.C.A. § 271(a).

Patents 291 328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most Cited

Cases

3,116,529, 3,291,300, 3,710,996, 3,738,034. Cited as prior art.

Patents 291 \$\iint\$328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most Cited

4,976,532, 5,144,345, 5,260,726, 5,521,911. Valid and infringed.

Patents 291 5 328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most Cited

Cases

5,141,104. Cited.

Trademarks 382T €=1800

382T Trademarks

382TXI **Trademarks** and Trade Adjudicated

382Tk1800 k. Alphabetical Listing. Most Cited Cases

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(Formerly 382k736) MAGNIVISION.

*1313 Peter T. Cobrin, Cobrin, Gittes & Samuel, of New York City, argued for plaintiffs-appellants. With him on the brief was *1314 Stephen E. Nagin, Nagin, Gallop & Figueredo, P.A., of Miami, Florida, of counsel was Oren J. Warshavsky. Donald W. Rupert, Mayer, Brown & Platt, of Chicago, Illinois, argued for defendants-cross appellants. With him on the brief were Robert S. Rigg and Lisa A. Schneider, of counsel on the brief were Richard L. Horn and Heather A. Libbey, Wilson & McIlvaine, of Chicago, Illinois, of counsel was Myles G. Cypen, Cypen & Cypen, of Miami, Florida.

Before: MAYER, Chief Judge, RICH, and RADER , Circuit Judges.

RADER, Circuit Judge.

This case involves patent, trademark, and trade dress infringement. After the United States District Court for the Southern District of Florida interpreted the claims, a jury found that VSI International, Inc. (VSI) had infringed several patents claiming specific hangers for displaying non-prescription eyeglasses. The jury also found trademark and trade dress infringement, and unfair competition. In addition, the jury found VSI's chairman and CEO, Myron Orlinsky, personally liable for these violations. Although Al-Site Corporation, now Magnivision, Inc. (Magnivision) FNI, prevailed on infringement, it appeals the district court's claim construction. On review, this court discerns errors in claim construction. Under a correct claim construction, the record contains VSI infringed substantial evidence that Therefore, this court Magnivision's patents. affirms the patent infringement finding. The record, however, does not contain substantial evidence to support the jury's findings of trademark and trade dress infringement, unfair competition, or personal liability for Myron Orlinsky. Therefore, this court reverses those judgments.

FN1. After this litigation began, American

Greetings Corporation acquired Al-Site Corporation, the named plaintiff in this case, and merged it with Magni-Tech Corporation to form Magnivision, Inc. The parties and this court, therefore, refer to the plaintiff as Magnivision.

I.

Magnivision and VSI both sell non-prescription eyeglasses. Magnivision is the assignee of U.S. Patent Nos. 4,976,532 (the '532 patent), 5,144,345 (the '345 patent), 5,260,726 (the '726 patent), and 5,521,911 (the '911 patent). These patents claim technology for displaying eyeglasses on racks. The claimed inventions allow consumers to try on eyeglasses and return them to the rack without removing them from their display hangers.

Magnivision sued VSI, as well as its chairman and CEO, Myron Orlinsky, in his individual capacity, for infringement of the Magnivision patents, for infringement of Magnivision's MAGNIVISION trademark and the trade dress of various products, and for unfair competition under Florida law. Six years after filing, the district court conducted a jury trial. After interpreting the claims, the district court instructed the jury to apply its construction of the claims to determine infringement.

The jury determined that one of VSI's products (the Version 1 hanger tag) literally infringed the '532 patent. The jury also determined that a second VSI product (the Version 2 hanger tag) did not literally infringe the '345, '726, and '911 patents, but did infringe those patents under the doctrine of equivalents. The jury further concluded that the Magnivision patents were not invalid under 35 U.S.C. § 103. Additionally, the jury found that VSI had infringed Magnivision's trademark and trade dress and had engaged in unfair competition. Finally, the jury imposed personal liability on Myron Orlinsky, making him jointly and severally liable for the damage award.

Following the jury verdict, Magnivision moved for judgment as a matter of law that the Version 2 hanger tag literally infringed the '345, '726, and '911 patents. VSI's post-trial motion sought to reverse

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all of the jury's determinations. The district*1315 court denied both motions and both parties appeal. Specifically, Magnivision challenges the district court's claim construction of the '345, '726, and '911 patents, arguing that the claims, if properly construed, would have been literally infringed by VSI's Version 2 hanger tag. VSI, on the other hand, contends that the district court's claim construction was correct but challenges the jury's determinations for lack of substantial evidence to support a verdict.

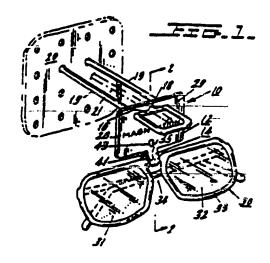
II.

[1] This court reviews the district court's denials of the motions for judgment as a matter of law using the same standards applied by the district court. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 975, 34 USPQ2d 1321, 1326 (Fed.Cir.1995), aff'd, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577, 38 USPQ2d 1461 (1996). This court will only upset a jury verdict if the record lacks substantial evidence to support the verdict. See Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1466, 43 USPQ2d 1481, 1484 (Fed.Cir.1997); Markman, 52 F.3d at 975.

Literal Infringement of the '532 patent

The jury determined that the Version 1 hanger tag literally infringes claims 8, 9, 14, 15, and 17 of the '532 patent. Claim 8, the independent claim from which the other infringed claims depend, claims the combination of a pair of eyeglasses and a hanger means for removably mounting the eyeglasses on a cantilevered support. The claim itself gives some structural definition of the hanger means as " including a body having aperture means adapted" for suspending the hanger and eyeglasses on the cantilevered support. Additionally, the hanger means includes an extension projecting from the bottom edge portion of the hanger body. This extension encircles the nose bridge of the eyeglasses. The claim specifies that "fastening means in engagement with said extension" hold the extension in a closed loop. Figure 1 from the '532 patent illustrates these claimed features:

FIG. 1.



The district court determined that the "fastening means" was a means-plus-function element subject to the interpretation requirements of 35 U.S.C. § 6 (1994). Consistent with determination, the trial court instructed the jury that "the fastening means ... is either a rivet or a button and hole arrangement as shown in the '532 patent or the structural equivalents thereof." Neither party challenges this part of the district court's claim construction.

*1316 [2] On appeal, VSI contends that its Version 1 hanger tag does not infringe because it does not include the "fastening means" required by claim 8. VSI's Version 1 hanger tag is a one-piece paper sticker having two large portions connected by a narrow extension. The entire back of the tag, including the extension, is coated with an adhesive. Backing paper covers the adhesive to prevent undesired adhesion. In use, a merchant removes the backing paper from the large portions of the tag. The extension (still covered with backing paper) then wraps around the nose bridge of the glasses. This wrapping glues the large portions together. In use, therefore, glue secures the two large portions of the tag to each other, leaving the narrow extension of the tag wrapped around the bridge of the

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eyeglasses.

The adhesive used by VSI is not identical to the fastening structure (namely, a rivet or button) described in the '532 patent. The jury, however, applying the rules of § 112, \P 6, determined that the VSI adhesive was equivalent to the structure disclosed in the specification. Accordingly, the jury returned a verdict of literal infringement of the '532 patent. VSI argues that substantial evidence does not support the jury's finding of literal infringement.

VSI first challenges the jury determination that adhesive is structurally equivalent to the mechanical fasteners disclosed in the specification of the '532 patent. Magnivision's technical expert, Anders, testified that, for one of ordinary skill in the art, it would be an insubstantial change "to substitute a rivet for a staple or for glue or for any other method that's standard in the [point of purchase] industry to maintain this loop as a closed loop." See Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc., 145 F.3d 1303, 1309, 46 USPQ2d 1752, 1756-57 (Fed.Cir.1998) ("The proper test [for determining equivalence under § 112, ¶ 6] is whether the differences between the structure in the accused device and any disclosed in the specification are insubstantial.... The question of known interchangeability is ... an important factor in determining equivalence [under § 112, ¶ 6]."). Mr. Anders further testified that the use of glue "in between the two layers of the body ... is an insubstantial change from the other structure ... which was one of a rivet. People in point of purchase displays use glue or rivets or staples to accomplish the same function." But see Chiuminatta, 145 F.3d at 1309 ("Almost by definition, two structures that perform the same function may be substituted for one another. The question of known interchangeability is not whether both structures serve the same function, but whether it was known that one structure was an equivalent of another."). Mr. Anders additionally testified that " equivalent fastening means could be a rivet, glue or staple or some such similar [structure]." This testimony constitutes sufficient evidence to sustain the jury's verdict that persons of ordinary skill in the art consider glue an equivalent structure to those disclosed in the specification for maintaining a closed loop.

As a fallback position, VSI argues that, even if the glue is an equivalent of the rivet or button, Magnivision presented no evidence that the glue was "in engagement" with the extension as claim 8 requires. On cross examination, Mr. Anders identified the middle section of the Version 1 hanger tag as the "extension" element. Mr. Anders also identified the glue as the "fastening means" element. Because VSI leaves the backing paper on its extension (presumably to prevent the tag from adhering to the eyeglasses), VSI argues that its extension does not engage the fastening means as required by the claims of the '532 patent.

VSI's argument is unpersuasive. The claims of the '532 patent only require that the fastening means be "in engagement with" the extension. As noted above, VSI coats the extension of its Version 1 hanger tag with glue-the fastening means identified by Mr. Anders. Furthermore, Mr. Anders' testimony explains that the extension and the glued portions are one integral piece. The jury could have interpreted*1317 his testimony to mean that the extension includes more than the narrow, middle portion of the Version 1 tag. Under this interpretation, the extension would also directly engage the glue fastening means. Alternatively, the jury could have determined that the extension is only the narrow portion of the Version 1 tag, but that the fastening means includes one of the two portions of the tag body in addition to the glue. Under any of these reasonable views of the accused product, the extension of the Version 1 hanger tag is in engagement with the glue fastening means as required by the claims.

[3] As the finder of fact, the jury receives deference for its function of weighing witness demeanor, credibility, and meaning. See Anderson v. City of Bessemer City, North Carolina, 470 U.S. 564, 575, 105 S.Ct. 1504, 84 L.Ed.2d 518 (1985) (factfinder entitled to deference on credibility determinations). Substantial evidence therefore supports the jury's verdict that VSI's Version 1 hanger tag literally infringes the '532 patent.

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Infringement of the '345, '726, and '911 Patents

The jury determined that VSI's Version 2 hanger tag and display rack did not literally infringe claims 1 and 2 of the '345 patent; claims 1 and 2 of the '726 patent; or claims 1, 2, and 3 of the '911 patent. The jury nevertheless found infringement of each of these claims under the doctrine of equivalents. argues that the district court Magnivision misconstrued these claims, and that, under the proper claim construction, VSI's products literally infringe these claims as a matter of law. VSI, on the other hand, embraces the district court's claim construction and argues that prosecution history estoppel precludes a finding of infringement under the doctrine of equivalents.

Claim 1 of the '345 patent and claim 1 of the '726 patent are similar. Both claim "[t]he combination of an eyeglass display member and an eyeglass hanger member." In each of these claims, this combination includes a "display member" with " cantilever support means" and "an eyeglass hanger member for mounting a pair of eyeglasses." Both claims further define the structure of the eyeglass hanger member. Claim 1 of the '345 patent describes the eyeglass hanger member as "made from flat sheet material," and having an "opening means formed ... below [its] upper edge." According to claim 1 of the '726 patent, the eyeglass hanger member has "an attaching portion attachable to a portion of said frame of said pair of eyeglasses to enable the temples of the frame [to be opened and closed]." Similarly, claim 2 of the '726 patent encompasses a "method of displaying eyeglass/hanger combinations ... the eyeglass hangers having an attaching portion attached to a portion of the frame of an associated pair of eyeglasses."

Claims 1, 2, and 3 of the '911 patent encompass a " combination of an eyeglass display member and an eyeglass contacting member." The '911 patent further describes the structure of the "eyeglass contacting member" as "having an encircling portion adapted to encircle a part of said frame of said pair of eyeglasses."

The district court construed the "eyeglass hanger

member" element of the '345 patent as a means-plus-function claim element subject to § 112, ¶ 6. Accordingly, the district court instructed the jury that "[t]he 'eyeglass hanger member for mounting a pair of eyeglasses' [in claim 1 of the '345 patent] is the body of the hanger disclosed in the '345 patent and its drawings and the structural equivalents thereof." The district court similarly interpreted the "eyeglass hanger member" element of the '726 patent. The district court instructed the jury that "[t]he 'eyeglass hanger member for mounting a pair of eyeglasses' [in claim 1 of the '726 patent] is the hanger disclosed in the '726 patent and its drawings as having a body, an aperture, and an attaching portion and the structural equivalents thereof."

*1318 With respect to the '911 patent, the district court concluded that the "eyeglass contacting member" was a means-plus-function element. The district court therefore instructed the jury that the " eyeglass contacting member" is "the hanger disclosed in the '911 patent and its drawings having a body and an aperture and an 'encircling portion', and the structural equivalents thereof."

[4] [5] This court reviews the district court's claim interpretation without deference. See Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 1454-56, 46 USPQ2d 1169, 1172-75 (Fed.Cir.1998) (en banc); Markman, 52 F.3d at 979-81. This court has delineated several rules for claim drafters to invoke the strictures of 35 U.S.C. § 112, ¶ 6. Specifically, if the word "means" appears in a claim element in combination with a function, it is presumed to be a means-plus-function element to which § 112, ¶ 6 applies. See Sage Prods., Inc. v. Devon Indus., Inc., 126 F.3d 1420, 1427, 44 USPQ2d 1103, 1109 (Fed.Cir.1997); Greenberg v. Ethicon Endo-Surgery, Inc., 91 F.3d 1580, 1583, USPO2d 1783, 1785 (Fed.Cir.1996). Nevertheless, according to its express terms, § 112, ¶ 6 governs only claim elements that do not recite sufficient structural limitations. See 35 U.S.C. § 112, ¶ 6. Therefore, the presumption that § 112, ¶ 6 applies is overcome if the claim itself recites sufficient structure or material for performing the claimed function. See Sage, 126 F.3d at 1427-28 (" [W]here a claim recites a function, but then goes on

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to elaborate sufficient structure, material, or acts within the claim itself to perform entirely the recited function, the claim is not in means-plus-function format."); York Prods., Inc. v. Central Tractor Farm & Family Ctr., 99 F.3d 1568, 1574, 40 USPQ2d 1619, 1623 (Fed.Cir.1996); Cole v. Kimberly-Clark Corp., 102 F.3d 524, 531, 41 USPO2d 1001, 1006 (Fed.Cir.1996).

[6] [7] Although use of the phrase "means for" (or " step for") is not the only way to invoke § 112, ¶ 6, that terminology typically invokes § 112, ¶ 6 while formulations generally do not. Greenberg, 91 F.3d at 1583-84. Therefore, when an element of a claim does not use the term "means, " treatment as a means-plus-function claim element is generally not appropriate. See Mas-Hamilton Group v. LaGard, Inc., 156 F.3d 1206, 1213-15, 48 USPQ2d 1010, 1016-18 (Fed.Cir.1998). However, when it is apparent that the element invokes purely functional terms, without the additional recital of specific structure or material for performing that the claim element may function. means-plus-function element despite the lack of express means-plus-function language. See, e.g., Cole, 102 F.3d at 531 ("[M]erely because an element does not include the word 'means' does not automatically prevent that element from being construed as a means-plus-function element."); Mas-Hamilton, 156 F.3d at 1213-15 (interpreting lever moving element" and "movable link member" under § 112, ¶ 6).

[8] Under this established analytical framework, the "eyeglass hanger member" elements in the claims of both the '345 and the '726 patents do not invoke § 112, ¶ 6. In the first place, these elements are not in traditional means-plus-function format. The word "means" does not appear within these although these claim elements. Moreover, elements include a function, namely, "mounting a pair of eyeglasses," the claims themselves contain sufficient structural limitations for performing those functions. As noted above, claim 1 of the '345 patent describes the eyeglass hanger member as " made from flat sheet material" with an "opening means formed ... below [its] upper edge." This structure removes this claim from the purview of § 112, ¶ 6. Similarly, according to claim 1 of the

'726 patent, the eyeglass hanger member has "an attaching portion attachable to a portion of said frame of said pair of eyeglasses to enable the temples of the frame [to be opened and closed]." This structure also precludes treatment as a means-plus-function claim element. The district court *1319 therefore improperly restricted the " eyeglass hanger member" in these claims to the structural embodiments in the specification and their equivalents.

[9] The district court also erred in interpreting the " attaching portion attachable to a portion of said frame of said pair of eyeglasses" element of claim 1 of the '726 patent as a means-plus-function element. It instructed the jury that the "attachable portion" is "a mechanically fastened loop that goes around the nose bridge of the glasses as disclosed in the specification, or the structural equivalent thereof." Because this claim element is also not in traditional means-plus-function form and supplies structural, not functional, terms, the trial court erred by applying § 112, ¶ 6 to this claim element. This error caused the district court to incorporate unduly restrictive structural limitations into the claim.

[10] For reasons similar to those discussed above with respect to the claim elements of the '345 and the '726 patents, the "eyeglass contacting member" element of the '911 patent claims is also not a means-plus-function element. Again, this claim element is not in traditional means-plus-function form. Furthermore, the claim itself recites sufficient structure for performing the recited function. Specifically, claim 1 of the '911 patent describes the "eyeglass contacting member" as " having an encircling portion adapted to encircle a part of said frame of said pair of eyeglasses to enable the temples of the frame to be selectively [opened and closed]." Similarly, claim 3 of the '911 patent describes the "eyeglass contacting member" as "having an attaching portion attachable to a portion of said frame of said eyeglasses." Therefore, the district court erred by applying § 112, ¶ 6 to these claim elements.

[11] Magnivision also complains that the district court erred in its construction of the language " means for securing a portion of said frame of said

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eyeglasses to said hanger member" in claim 1 of the '345 patent. With respect to this element, the district court instructed the jury that "[t]he 'means for securing' limitation is a mechanically fastened loop that goes around the nose bridge of the glasses. .. or an equivalent thereof." The district court went on, however, to instruct the jury that "[t]he means for securing can be formed from a separate extension or integral extension and includes either the rivet fastener or the button and hole fastener." Magnivision argues that the district court should have included the phrase "or equivalents thereof" after "button and hole fastener" in its instruction to the jury. Absent this and the other claimed errors in the district court's interpretation of claim 1 of the '345 patent, Magnivision argues that the jury would have found literal infringement rather than infringement under the doctrine of equivalents.

The "means for securing" claim element is in conventional means-plus-function format without specific recital of structure and therefore invokes § 112, ¶ 6. The jury's finding of infringement of claim 1 of the '345 patent under the doctrine of equivalents indicates that the jury found every element of the claim literally or equivalently present in the accused device. The question before this court, therefore, is whether the jury's finding that the accused structure was equivalent to the "means for securing" element under the doctrine of equivalents, also indicates that it is equivalent structure under § 112, ¶ 6.

This court has on several occasions explicated the distinctions between the term "equivalents" found in § 112, ¶ 6 and the doctrine of equivalents. See, e.g., Valmont Indus., Inc. v. Reinke Mfg. Co., 983 F.2d 1039, 1042-44, 25 USPQ2d 1451, 1453-56 (Fed.Cir.1993); Chiuminatta, 145 F.3d at 1310; Alpex Computer Corp. v. Nintendo Co., 102 F.3d 1222, 40 USPQ2d 1667, 1673-74 (Fed.Cir.1996); Dawn Equipment Co. v. Kentucky Farms Inc., 140 F.3d 1009, 1018-23, 46 USPQ2d 1109, 1115-18 (Fed.Cir.1998) (Plager, J., additional views) (Newman, J., additional views) (Michel, J., additional views). Indeed, the *1320 Supreme Court recently acknowledged distinctions between equivalents as used in § 112, ¶ 6 and the doctrine of equivalents. See Warner-Jenkinson Co. v.

Hilton Davis Chem. Co., 520 U.S. 17, 27, 117 S.Ct. 1040, 1048, 137 L.Ed.2d 146, 41 USPQ2d 1865, 1870-71 (1997) ("[Equivalents under § 112, ¶ 6] is an application of the doctrine of equivalents in a restrictive role, narrowing the application of broad literal claim elements. [Section 112, ¶ 6] was enacted as a targeted cure to a specific problem.... The added provision, however, is silent on the doctrine of equivalents as applied where there is no literal infringement.")

[12] Section 112, ¶ 6 recites a mandatory procedure for interpreting the meaning of a meansor step-plus-function claim element. These claim limitations "shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof." 35 U.S.C. § 112, ¶ 6. Thus, § 112, ¶ 6 procedures restrict a functional claim element's "broad literal language ... to those means that are 'equivalent' to the actual means shown in the patent specification." Warner-Jenkinson, 117 S.Ct. at 1048. Section 112, ¶ 6 restricts the scope of a functional claim limitation as part of a literal infringement analysis. See Pennwalt Corp. v. Durand-Wayland, Inc., 833 934, 4 USPQ2d 1737, 1739 F.2d 931, (Fed.Cir.1987). Thus, an equivalent under § 112, ¶ 6 informs the claim meaning for a literal infringement analysis. The doctrine of equivalents, on the other hand, extends enforcement of claim terms beyond their literal reach in the event "there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." Warner-Jenkinson, 117 S.Ct. at 1045.

[13] [14] One important difference between § 112, ¶ 6 and the doctrine of equivalents involves the timing of the separate analyses for an "insubstantial change." As this court has recently clarified, a structural equivalent under § 112 must have been available at the time of the issuance of the claim. See Chiuminatta, 145 F.3d at 1310. An equivalent structure or act under § 112 cannot embrace technology developed after the issuance of the patent because the literal meaning of a claim is fixed upon its issuance. An "after arising equivalent" infringes, if at all, under the doctrine of equivalents. See Warner-Jenkinson, 117 S.Ct. at

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1052; Hughes Aircraft Co. v. U.S., 140 F.3d 1470, 1475, 46 USPO2d 1285, 1289 (Fed.Cir.1998). Thus, the temporal difference between patent issuance and infringement distinguish an equivalent under § 112 from an equivalent under the doctrine of equivalents. See Chiuminatta, 145 F.3d at 1310. In other words, an equivalent structure or act under § 112 for literal infringement must have been available at the time of patent issuance while an equivalent under the doctrine of equivalents may arise after patent issuance and before the time of infringement. See Warner-Jenkinson, 117 S.Ct. at 1053. An "after-arising" technology could thus infringe under the doctrine of equivalents without infringing literally as a \S 112, \P 6 equivalent. FN2 Furthermore, under § 112, ¶ 6, the accused device must perform the identical function as recited in the claim element *1321 while the doctrine of equivalents may be satisfied when the function performed by the accused device is only substantially the same. See Cybor, 138 F.3d at 1456; Hughes Aircraft, 140 F.3d at 1475.

> FN2. These principles, as explained in Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc., 145 F.3d 1303, 46 USPQ2d 1752 (Fed.Cir.1998), suggest that title 35 will not produce an "equivalent of an equivalent" by applying both § 112, ¶ 6 and the doctrine of equivalents to the structure of a given claim element. A proposed equivalent must have arisen at a definite period in time, i.e., either before or after patent issuance. If before, a § 112, ¶ 6 structural equivalents analysis applies and any analysis for equivalent structure under the doctrine of equivalents collapses into the § 112, ¶ 6 analysis. If after, a non-textual infringement analysis proceeds under the doctrine of equivalents. Patent policy supports application of the doctrine of equivalents to a claim element expressed in means-plus-function form in the case of "after-arising" technology because a patent draftsman has no way to anticipate and account for later developed substitutes for a claim element. Therefore, the doctrine of equivalents

appropriately allows marginally broader coverage than § 112, ¶ 6.

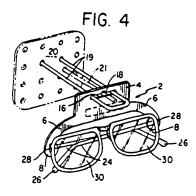
[15] Although § 112, ¶ 6 and the doctrine of different in purpose equivalents are administration, "a finding of a lack of literal infringement for lack of equivalent structure under a means-plus-function limitation may preclude a finding of equivalence under the doctrine of equivalents." Chiuminatta, 145 F.3d at 1311. Both equivalence analyses, after all, apply "similar analyses of insubstantiality of the differences." Id. This confluence occurs because infringement requires, either literally or under the doctrine of equivalents, that the accused product or process incorporate each limitation of the claimed invention. See Warner-Jenkinson, 117 S.Ct. at 1049; Pennwalt, 833 F.2d at 935. Therefore, if an accused product or process performs the identical function and yet avoids literal infringement for lack of a § 112, ¶ 6 structural equivalent, it may well fail to infringe the same functional element under the doctrine of equivalents. See Chiuminatta, 145 F.3d at 1311. This same reasoning may be applied in reverse in certain circumstances. Where, as here, there is identity of function and no after-arising technology, a means-plus-function claim element that is found to be infringed only under the doctrine of equivalents due to a jury instruction failing to instruct on § 112, ¶ 6 structural equivalents is also literally present in the accused device.

VSI's Version 2 hanger tag has a central body and two arms, with one arm extending from each side of the body. Each arm has a hole near the end for receipt of an eyeglasses temple. The body also has an aperture through which a cantilever rod can be placed so the hanger tag can be hung from a display rack. VSI's Version 2 hanger tag is the subject of U.S. Patent No. 5,141,104 (the '104 patent). Figure 4 of the '104 patent illustrates these features.

FIG. 4.

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As noted above, the doctrine of equivalents and structural equivalents under § 112, ¶ 6, though different in purpose and administration, can at times render the same result. In this case, the jury found infringement under the doctrine of equivalents. This finding presupposes that the jury found an equivalent for each element of the claimed invention, including the "means for securing." The holes in the arms of VSI's Version 2 hanger tag secure a portion of the eyeglasses frame (the temples) to the hanger member and therefore perform the identical function of the claim element in question. The jury was instructed that the " means for securing" disclosed in the '345 patent "is a mechanically fastened loop that ... can be formed from a separate extension or integral extension and includes either the rivet fastener or the button and hole fastener." Based on this instruction, the jury found *1322 that the holes in the arms of the Version 2 hanger tag were equivalent to the mechanically fastened loop of the '345 patent under the doctrine of equivalents.

The parties do not dispute that the holes in the arms of the accused device perform a function identical to the extension of the patented device. Furthermore, the holes do not constitute an after-arising technology. Because the functions are identical and the holes are not an after-arising technology, the jury's finding of infringement under the doctrine of equivalents indicates that the jury found insubstantial structural differences between the holes in the arms of the Version 2 hanger tag

and the loop of the '345 patent claim element. That finding is also sufficient to support the inference that the jury considered these to be structural equivalents under § 112, ¶ 6. For these reasons, any perceived error in the district court's jury instruction regarding the "means for securing" is, at most, harmless.

[16] Magnivision also argues that the district court improperly construed the "opening means" of claim 1 of the '345 patent. The court instructed the jury that "[t]he 'opening means' is the elongated slot having a notch as described and depicted in the '345 patent, and the structural equivalents thereof." Citing Al-Site Corp. v. Bonneau Co., 22 F.3d 1107, USPQ2d 1136, 1139 (Fed.Cir.1994), Magnivision argues that this court has already construed this structure to be "an enclosed hole and equivalents thereof."

For several reasons, Magnivision's reliance on Bonneau fails. First, as Magnivision admits, in Bonneau, this court construed claim 8 of the '532 patent, not the claims of the '345 patent. These claims have different language and different meanings. Furthermore, Magnivision did not inform the trial court that Bonneau was a non-precedential opinion (in which Magnivision lost), which may only be cited for its issue preclusive effect against Magnivision. Finally, in Bonneau, Magnivision argued for a broader claim construction than that eventually adopted by this court. This litigation record gives no reason to think that the court rejected the district court's construction in this case, nor any reason to deny VSI the opportunity to seek a narrower construction. With regard to claim 1 of the '345 patent, the claim element "opening means for receiving cantilever support means and securing a horizontal orientation for the eyeglasses" invokes § 112, ¶ 6, and the district court correctly determined the scope of the claim.

[17] In a further attempt to overturn the jury verdict of infringement under the doctrine of equivalents with respect to the '345, '726, and '911 patents, VSI relies on prosecution history estoppel. This court has reviewed VSI's prosecution history estoppel argument and finds it unpersuasive. To overcome

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prior art objections by the Examiner, Magnivision amended what became claim 8 of the '532 patent to require that the extension project from the bottom edge portion of the hanger tag. Citing Mark 1 Marketing Corp. v. R.R. Donnelley & Sons Co., 66 F.3d 285, 291, 36 USPQ2d 1095, 1100 (Fed.Cir.1995), VSI argues that because all of arose from Magnivision's patents applications, the same prosecution history estoppel applies to them as well. VSI therefore contends that because the arms of its Version 2 hanger tag extend from the sides of the body of the tag, it cannot infringe the claims of these patents under the doctrine of equivalents as restricted by prosecution history estoppel. While in some cases, the prosecution history of a related application may limit application of the doctrine of equivalents in a later filed patent, in this case the specific limitation added in the claims of an earlier issued patent is not present in the claims of the later issued patents. The '345, '726, and '911 patents all have limitations not found in the '532 patent and did not necessarily require the specific limitation added to the claims of the '532 patent to be patentable. The specific limitations added to gain allowance of the '532 patent are not included in and *1323 are therefore not relevant to determining the scope of the claims of the later issued patents.

In sum, the district court erred by interpreting several of the claim elements in the '345, '726 and '911 patents as means-plus-function elements subject to § 112, ¶ 6. Because, properly construed, these claims do not call for interpretation under § 112, ¶ 6, the district court's reading unnecessarily limited their scope. This court has cautioned against incorporating unwarranted functional or structural limitations from the specification into the claims. See Transmatic, Inc. v. Gulton Indus., Inc., 53 F.3d 1270, 1277, 35 USPQ2d 1035, 1041 court's district (Fed.Cir.1995). Despite the unwarranted restriction of the claims, the jury found infringement under the doctrine of equivalents. Although a reasonable dispute as to the application of the correctly interpreted claims to the accused structure prevents a determination of literal infringement as a matter of law, because the jury found infringement under the trial court's more restricted reading of the claims, this court need not remand for an infringement determination according to this court's broader claim interpretation. Proceeding claim element by claim element, the jury has already found infringement. This court's correction of the claim scope does not disturb that determination.

Validity of the '532, '345, '726, and '911 patents

VSI challenges the validity of all four Magnivision patents under 35 U.S.C. § 103. Specifically, VSI asserts that these patents are obvious in light of U.S. Patent No. 3,738,034 (the Seaver patent) or the 1984 B & G catalog and the knowledge of one of ordinary skill in the art. VSI also asserts obviousness based on the Rosen patent (U.S. Patent No. 3,291,300), the Pacelli patent (U.S. Patent No. 3,116,529), and German Design Patent No. G 8,212,306.3 U1 (the German patent). On appeal, VSI particularly urges that the Cool-Ray catalogs (which depict the commercial embodiment of the Seaver patent), when viewed with the knowledge of one of ordinary skill in the art, render all of the disputed claims invalid for obviousness. The jury considered and rejected VSI's claims of invalidity.

[18] [19] Although the determination of obviousness is ultimately a legal conclusion, it rests on underlying factual determinations. See Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 USPQ 459, 467 (1966). Issued patents have a strong presumption of validity in infringement proceedings. See 35 U.S.C. § 282 (1994). Hence, an accused infringer who defends on grounds of patent invalidity bears the burden of showing patent invalidity by clear and convincing evidence. See Monarch Knitting Mach. v. Sulzer Morat GMBH, 139 F.3d 877, 881, 45 USPQ2d 1977, 1981 (Fed.Cir.1998).

[20] In a challenge based on obviousness under 35 U.S.C. § 103, the person alleging invalidity must show prior art references which alone or combined with other references would have rendered the invention obvious to one of ordinary skill in the art at the time of invention. See Dennison Mfg. Co. v. Panduit Corp., 475 U.S. 809, 810, 106 S.Ct. 1578, 89 L.Ed.2d 817, 229 USPQ 478, 479 (1986);

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Rockwell Int'l Corp. v. United States, 147 F.3d 1358, 1364, 47 USPQ2d 1027, 1032 (Fed.Cir.1998) . The "presumption of validity under 35 U.S.C. § 282 carries with it a presumption that the Examiner did his duty and knew what claims he was allowing." Intervet Am., Inc. v. Kee-Vet Labs., Inc., 887 F.2d 1050, 1054, 12 USPQ2d 1474, 1477 (Fed.Cir.1989) . Therefore, the challenger's "burden is especially difficult when the prior art was before the PTO examiner during prosecution of the application." Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1467, 15 USPQ2d 1525, 1527 (Fed.Cir.1990).

[21] The party seeking patent invalidity based on obviousness must also show some motivation or suggestion to combine *1324 the prior art teachings. See In re Rouffet, 149 F.3d 1350, 1355, 47 USPQ2d 1453, 1457 (Fed.Cir.1998); Motorola, 121 F.3d at 1472. A suggestion or motivation to combine generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. See Rouffet, 149 F.3d at 1355.

[22] In this case, the United States Patent and Trademark Office (the PTO) considered nearly all the prior art that VSI asserts renders Magnivision's patents obvious. The PTO considered the Seaver patent during its prosecution of the applications for each of the '345, '726, and '911 patents. The B & G catalog was before the PTO in the application that led to the '911 patent. Moreover, the structure of the B & G reference appears in the Smilow Patent (U.S. Patent No. 3,710,996) which was cited against each of these patents. All of the other references, except the Rosen patent, which is similar to the German patent, were before the PTO in the examinations of one or more of the Magnivision patent applications.

The Seaver patent is the most pertinent prior art. The Seaver patent discloses a security tag for eyeglasses. The Seaver tag is used as an anti-theft device in conjunction with prior art displays. In these displays, the temples of the eyeglasses are not folded, but rather extend through openings in the display. The Seaver security tag is not a hanger display tag and is not designed nor intended to have a cantilevered support extend through it. Neither does the Seaver patent suggest stacking a plurality of folded eyeglasses on a cantilevered support. The Seaver security tag does, however, disclose some elements of the claimed invention, such as a loop that secures the tag to the eyeglasses. Nevertheless, although the Seaver patent discloses some of the elements recited in the Magnivision patents' claims, it does not disclose the display member, the cantilevered support, or the aperture for mounting the hanger tag on the cantilevered support.

[23] VSI argues that it would have been obvious to one of ordinary skill in the art to punch a hole in the Seaver security tag and hang it from a cantilevered support. VSI points to the problems in the art and the Rosen, German, and Pacelli patents to support this conclusion. VSI is unable, however, to point to any specific teaching or suggestion for making this combination. VSI instead relies on what it presumes is the level of knowledge of one of ordinary skill in the art at the time of the invention to supply the missing suggestion to combine. In the first place, the level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness. Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment. See W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed.Cir.1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). Skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process. See Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed.Cir.1991).

The level of skill in the art is a factual

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determination. See Graham, 383 U.S. at 17-18. Because the jury considered and rejected VSI's challenge on this grounds, it evidently concluded that one of ordinary skill in the art would not have known to make this combination. This factual finding is supported by substantial evidence. *1325 VSI's argument in this regard is therefore an impermissible effort at hindsight recreation. See Grain Processing Corp. v. American Maize-Prods. Co., 840 F.2d 902, 5 USPQ2d 1788, 1792 (Fed.Cir.1988).

The German patent (and the similar Rosen patent) disclose theft-resistant display tags for sunglasses. These display tags are essentially plastic cards with holes for receiving the temples of the sunglasses and another hole for hanging them on a cantilevered support. In some ways, they are similar to the Magnivision patents. In other ways, however, they are quite different. Dr. Chrycy, an expert optometrist, explained that the device disclosed in the German patent would not be suitable as a display tag for reading eyeglasses because it does not allow a person trying them on to determine if they are the correct strength. The plastic card of the German display tag interferes with the proper fit of the eyeglasses and therefore would result in visual distortions or blurring. The Rosen patent has similar drawbacks.

The Pacelli patent also discloses a theft-resistant tag for displaying sunglasses. To secure the glasses, the Pacelli patent uses a sheet of plastic which covers the frame and impairs the view of a person trying on the glasses. Dr. Chrycy testified that this would result in alteration of the view through the lenses and would therefore not serve as a reading glasses display tag.

The B & G catalog primarily discloses belt hangers. Although the catalog discloses possible use of these hangers for eyeglasses, Mr. Hallerman, another expert, testified that they could not be used effectively for holding eyeglasses because they lacked the necessary stability.

Magnivision further supports the jury's factual findings related to nonobviousness with record evidence of secondary considerations. These secondary considerations, such "as commercial success, long felt but unresolved needs, failure of others, etc.," also provide objective proof of nonobviousness. Dennison, 475 U.S. at 810. The record shows the commercial success of the claimed invention, including demonstration of a nexus between the commercial success and the patented invention, and evidence of a long felt need for a solution to several of the problems addressed by the invention.

Mort Nyman, an expert in the design, development and marketing of nonprescription reading glasses, testified regarding the problems experienced with prior art eyeglass hangers. He further testified that efforts prior to Magnivision's invention were unsuccessful in solving these problems. Prior art displays were bulky and incapable of displaying several pairs of eyeglasses at the same vertical position. Prior art displays contained openings for insertion of the temples of the eyeglasses and therefore allowed only one pair of eyeglasses per vertical position. Because fewer glasses fit on the prior art displays, vendors had to frequently refill the display rack. Moreover, prior art theft-resistant displays prevented potential customers from effectively trying on the eyeglasses.

Magnivision overcame the deficiencies of the prior art by developing a hanger tag which does not interfere with the opening and closing of the temples or distort the view of the user through the eyeglasses. Furthermore, Magnivision's hanger tags featured an aperture for mounting on a cantilevered support. In this way, several pairs of eyeglasses of the same magnification strength could fit on the display together. Due to this design, store managers no longer needed to frequently refill the eyeglass display rack. For these reasons, the theft-resistant hanger tags disclosed in the Magnivision patents satisfied the long-felt needs of the industry.

Magnivision also presented evidence of commercial success, which further tended to establish the nonobviousness of the claimed inventions. Particularly, Magnivision presented evidence showing that all of the retail chains that sold Magnivision glasses wanted to switch from the prior

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art displays to Magnivision's patented displays. evidence*1326 also presented showing that as a direct result of Magnivision's patented inventions, the number of locations selling Magnivision eyeglasses more than doubled. This of commercial success evidence strengthened the district court's determination that the Magnivision patents were not obvious. The factual findings made by the jury underlying this determination are supported by substantial evidence.

Based on the evidence presented at trial, the jury found that VSI failed to provide clear and convincing evidence of obviousness. Because the finding of obviousness rests on underlying factual determinations, which the jury found adverse to VSI, the district court correctly concluded that the Magnivision patents are not invalid under 35 U.S.C. § 103.

Trade Dress Infringement

[24] [25] For areas of law, such as trademark and trade dress infringement, which are not unique to this court's jurisdiction, this court applies the law of the pertinent regional circuit, in this case the United States Court of Appeals for the Eleventh Circuit. See Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1574, 37 USPQ2d 1626, 1631 (Fed.Cir.1996). Under Eleventh Circuit law, a finding of trademark and trade dress infringement is a question of fact. See AmBrit, Inc. v. Kraft, Inc., 812 F.2d 1531, 1535 (11th Cir.1986). A jury verdict of trademark or trade dress infringement is therefore reviewed for substantial evidence. See John H. Harland Co. v. Clarke Checks, Inc., 711 F.2d 966, 973, 219 USPQ 515, 522 (11th Cir.1983) . Legal determinations of the district court, however, receive no deference on review. See Lucero v. Trosch, 121 F.3d 591, 599 (11th Cir.1997).

[26] [27] Trade dress protection embraces the total image of the product including such factors as the size, shape, and color of the product's packaging and appearance. See Two Pesos, Inc. v. Taco Cabana, Inc., 505 U.S. 763, 765 n. 1, 112 S.Ct. 2753, 120 L.Ed.2d 615, 23 USPQ2d 1081, 1082 n.

1 (1992). To prove trade dress infringement, the plaintiff must show: (1) the inherent distinctiveness or secondary meaning of its trade dress, (2) the essential nonfunctionality of its trade dress, and (3) the likelihood of consumer confusion as to origin, sponsorship, or approval due to similarity between its and the defendant's trade dress. See University of Fla. v. KPB, Inc., 89 F.3d 773, 776-77, 39 USPQ2d 1603, 1605 (11th Cir.1996). Because this is a conjunctive test, failure to prove even one of these elements precludes a showing of trade dress infringement. Therefore, the defendant can secure a summary judgment of noninfringement by demonstrating that the plaintiff cannot show any element of the cause of action.

[28] [29] [30] [31] As mentioned above, protection hinges on the distinctiveness or secondary meaning of the trade dress. Distinctive trade dress enables consumers to distinguish a product from others and identify that product with its source. See id. at 776 n. 5. The Eleventh Circuit gauges distinctiveness based on whether trade dress "[is] a 'common' basic shape or design, whether it [is] unique or unusual in a particular field, [and] whether it [is] a mere refinement of a commonly adopted and well-known form of ornamentation for a particular class of goods viewed by the public as a dress or ornamentation for the goods." Id. (quoting AmBrit, 812 F.2d at 1536). Trade dress can also satisfy this requirement by showing secondary meaning, or a " connection in the consumer's mind between the mark and the product's producer, whether that producer is known or unknown." Id. The plaintiff may show secondary meaning in several ways. The plaintiff may show secondary meaning with consumer surveys and with evidence of lengthy and uniform display of the dress. See Conagra, Inc. v. Singleton, 743 F.2d 1508, 1513, 224 USPQ 552, 555-56 (11th Cir.1984). The plaintiff may also show secondary meaning with evidence of the plaintiff's efforts-usually through advertising*1327 -to establish in the minds of the consumers a connection between the trade dress and its product. See id. Finally, the plaintiff may use other evidence showing consumers' association of the trade dress with the plaintiff or its product to prove secondary meaning. See id.

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1161, 1165 (1995).

[32] Trade dress must also be primarily nonfunctional. A trade dress is functional "if it is essential to the use or purpose of the article or if it affects the cost or quality of the article," Inwood Labs., Inc. v. Ives Labs., Inc., 456 U.S. 844, 850 n. 10, 102 S.Ct. 2182, 72 L.Ed.2d 606, 214 USPQ 1, 4 n. 10 (1982), such that its protection would place a competitor at a significant disadvantage, see Qualitex Co. v. Jacobson Prods. Co., 514 U.S. 159, 165, 115 S.Ct. 1300, 131 L.Ed.2d 248, 34 USPQ2d

[33] Trade dress protection also requires evidence of a likelihood of confusion between the plaintiff's and the defendant's trade dress. Determining whether a likelihood of confusion exists requires weighing several factors: (1) the nature of the plaintiff's mark, (2) the similarity of the marks, (3) the similarity of the products the marks represent, (4) the similarity of the parties' retail outlets and customers, (5) the similarity of the parties' advertising, (6) the defendant's intent to copy or imitate the plaintiff's mark, and (7) the extent of actual confusion. See Wesco Mfg., Inc. v. Tropical Attractions of Palm Beach, Inc., 833 F.2d 1484, 1488, 5 USPQ2d 1190, 1193-94 (11th Cir.1987).

The jury found that VSI infringed Magnivision's display card and blister pack trade dress, Magnivision's color coding trade dress, and Magnivision's eyeglass styles and colors trade dress. Each of these trade dresses requires separate analysis.

Display Card/Blister Pack Trade Dress

[34] [35] Magnivision used a particular display card and blister pack to market its hand-held magnifiers. The display card contains a bold red stripe along its right-hand side and a gray and white cross-hatched background over the remainder of the card. As evidence of distinctiveness of this trade dress, Magnivision presented testimony by Morton Nyman, its president, "that Magnivision is the only company that used this design until it was copied by VSI." Magnivision's use of a display design different from others, however, does not suffice to show distinctiveness in the minds of consumers.

Rather, sole use of a design is a preliminary step for a descriptive trade dress to acquire distinctiveness and secondary meaning. See In re Owens-Corning Fiberglas Corp., 774 F.2d 1116, 1125, 227 USPQ 417, 422 (Fed.Cir.1985) ("An evidentiary showing of secondary meaning ... includes evidence of the trademark owner's method of using the mark, supplemented by evidence of the effectiveness of such use to cause the purchasing public to identify the mark with the source of the product.").

In this case, Magnivision did not supply evidence of distinctiveness or secondary meaning. Although Magnivision presented some testimony of sole use, the facts belie any acquisition of secondary meaning. A review of some factors related to secondary meaning show the inadequacy of Magnivision's showing. For instance, with regard to the length and manner of the trade dress use, the record shows that Magnivision used its display design for only two years. Moreover, Magnivision discontinued use of the design two years before VSI put their allegedly infringing packaging on the market. With respect to the nature and extent of advertising and promotion-the efforts by the plaintiff to promote a conscious connection in the public's mind between the trade dress and the plaintiff's business-the record shows that promotional Magnivision made significant expenditures. None of these expenditures or activities, however, was tied to the display card trade dress. The record also contained no evidence that consumers actually recognized Magnivision's allegedly distinctive trade dress for hand-held magnifiers.

*1328 Without evidence of distinctiveness or secondary meaning beyond its assertion of sole use, no reasonable juror could have found that Magnivision's design had acquired secondary meaning. Hence, Magnivision did not supply enough evidence of this first requirement for trade dress infringement to support the jury's verdict. This conclusion alone precludes a finding of trade infringement on the display card. Nonetheless, a brief review of the evidence of likelihood of confusion underscores this court's determination.

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As mentioned earlier, the likelihood of confusion analysis requires consideration of several factors. In this case, although the consumers and markets were similar, the packaging was not. Comparison of the two packages shows distinct differences in appearance. Specifically, both the graphics and color scheme are different. VSI's accused packaging does not contain either the bold red stripe or the cross-hatched gray and white background of Magnivision's asserted trade dress. VSI's display card contains a dark black band across the top, with gray and blue stripes covering the remainder of the card. Additionally, VSI's ACURAVISION trademark is prominently displayed in the top black band. Furthermore, VSI's accused display card contains other distinctive features such as a broad blue arrow and MAGNA-DOT trademark under the lens of the magnifier.

Perhaps because of the substantial differences between the accused packaging and Magnivision's asserted trade dress, Magnivision did not produce any evidence of actual customer confusion. The record as a whole lacks evidence to support the jury's finding of a likelihood of consumer confusion.

No reasonable juror could have found trade dress infringement of the display cards. Because the district court based its injunction prohibiting similar display cards on other accessories on the jury's finding of display card infringement, the district court abused its discretion in enjoining the use of the accessory packages.

Color Coding Trade Dress

[36] The jury also found that VSI had infringed Magnivision's trade dress in its color coding system. This alleged trade dress is an array of horizontal color-coded stripes on Magnivision's eyeglass hanger tags which identify the power of the glasses. Under this system, the hangers for eyeglasses of a particular power would feature a particular color. Eyeglasses of a different power would hang from a tag with a different color.

[37] At the outset, the record does not contain

sufficient evidence to show any distinctiveness or secondary meaning for Magnivision's color coding system. Color itself is not inherently distinctive. See Qualitex, 514 U.S. at 163 ("[O]ver time, customers may come to treat a particular color on a product or its packaging (say, a color that in context seems unusual, such as pink on a firm's insulating material or red on the head of a large industrial bolt) as signifying a brand."). Thus, to support its finding of infringement, the jury must have found secondary meaning in this color-coding system. The record, however, discloses no evidence to support such a finding.

[38] Other companies used color coding to market non-prescription reading glasses for many years. Thus, Magnivision has a significant burden to show that its particular color-coding system had acquired source-identifying significance in the minds of the consuming public. Magnivision's burden becomes almost insurmountable in light of the evidence showing that its coloring system changed from time "Absent a specifically time. color-definite, and stable visual appearance, an alleged trade dress cannot receive protection." Keystone Camera Prods. Corp. v. Ansco Photo-Optical Prods. Corp., 667 F.Supp. 1221, 1229, 3 USPQ2d 1797, 1802 (N.D.III.1987) (emphasis added).

Although the actual colors Magnivision associated with particular diopter strengths did not change significantly, *1329 Magnivision changed its coding method several times. At various times Magnivision used three different ways to signify diopter strength: the color of the diopter numbers, a horizontal stripe of color across one side of the tag, or a colored rectangle. Without a stable visual appearance and absent any other evidence of consumer identification of the Magnivision's color-coding system, no reasonable juror could conclude that the stripe of color now asserted as a trade dress has acquired secondary meaning.

Furthermore, even if Magnivision could show secondary meaning in its color coding system, color coding cannot act as an indicator of source because it is primarily functional. See Two Pesos, 505 U.S. at 775 (trade dress is functional if it "is one of a

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limited number of equally efficient options available to competitors and free competition would be hindered by according the design trademark protection"); Spraying Sys. Co. v. Delavan, Inc., 762 F.Supp. 772, 781, 19 USPQ2d 1121, 1128 (N.D.III.1991), aff'd, 975 F.2d 387, 24 USPQ2d 1181 (7th Cir.1992) ("color coding as an identification system is clearly functional"). In this case, the record shows that Magnivision used color coding to indicate diopter strength, not to indicate source. Magnivision itself stated that color coding allows the racks to be serviced more easily, aids consumers in selecting the correct diopter, and reduces the time and cost of restocking the glasses. Additionally, as noted earlier, color coding serves these same cost-saving functions for many competitors in the non-prescription eyeglass industry. To give one competitor an exclusive

Because color coding is primarily functional, the record refutes the jury's verdict of trade dress infringement of Magnivision's color coding system. On the basis of this record, this court concludes that no reasonable juror could have found trade dress infringement of Magnivision's color coding scheme because of the functional nature of the trade dress and the lack of showing of secondary meaning. This court, therefore, need not proceed to examine the likelihood of confusion. Because the jury verdict of trade dress infringement lacks substantial evidence, the district court abused its discretion by enjoining VSI's use of its hanger tag labels based on trade dress infringement.

right to practice color-coding would give it a

significant advantage over other companies.

Eyeglass Styles and Colors Trade Dress

[39] The jury also found that VSI infringed the trade dress of six of Magnivision's eyeglass styles. Once again, however, the record contains insufficient evidence that Magnivision's colors or styles were inherently distinctive or possessed secondary meaning. Mr. Nyman testified that Magnivision purchased its allegedly distinctive styles from publicly available molds. VSI purchased its accused styles from publicly available stock as well. This evidence of the public availability of Magnivision's product raises significant hurdles to a finding that its styles are inherently distinctive as an indicator of source. See Mana Prods., Inc. v. Columbia Cosmetics Mfg., Inc., 65 F.3d 1063, 1070, 36 USPQ2d 1176, 1180 (2nd Cir.1995) (When similar packaging can be purchased by other companies and is publicly available, "it defies simple logic to suggest that the packaging was inherently distinctive.").

Magnivision produced no evidence of secondary meaning. The record demonstrates that it changed its styles to suit demand. Constantly changing styles rarely demonstrate the stability necessary for the public to identify those particular characteristics with a particular source. See, e.g., Keystone, 667 F.Supp. at 1226 (identifying the significant weakness in the plaintiff's trade dress claim as being that the Le Clic "look" was "nothing more than a reflection of the fashion trends taking place generally in the marketplace of youthful consumers."). Thus, the record shows that the publicly constantly changing styles available, Magnivision's eyeglasses lacked secondary meaning.

Without *1330 inherent distinctiveness secondary meaning, Magnivision's eyeglass styles and colors lacked a protectable trade dress. Absent a protectable trade dress, no reasonable juror could find trade dress infringement.

Trademark Infringement of the MAGNIVISION mark

[40] [41] The jury found that VSI's mark MAGNA. DOT infringes Magnivision's MAGNIVISION mark. To prove trademark infringement, a trademark owner must show a likelihood that consumers would confuse the defendant's mark with the protected mark. See Dieter v. B & H Indus. of Southwest Fla., Inc., 880 F.2d 322, 326, 11 USPQ2d 1721, 1723 (11th Cir.1989). The Eleventh Circuit identifies several factors which contribute to a likelihood of confusion finding: (1) the nature of the plaintiff's mark, (2) the similarity of the marks, (3) the similarity of the products represented by the marks, (4) the similarity of the retail outlets and consumers, (5) the nature and

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(Cite as: 174 F.3d 1308)

extent of the parties' advertising, (6) the defendant's intent to copy the plaintiff's mark, and (7) the extent of actual confusion. See Wesco, 833 F.2d at 1488; Coach House Restaurant, Inc. v. Coach and Six Restaurants Inc., 934 F.2d 1551, 1561, 19 USPQ2d 1401, 1409 (11th Cir.1991). Other relevant factors include the strength of the marks, the number and nature of similar marks in use on similar goods, the nature and extent of any actual confusion and the length of time during and conditions under which there has been concurrent use without evidence of actual confusion. See In re E.I. DuPont DeNemours & Co., 476 F.2d 1357, 1361, 177 USPQ 563, 567 (CCPA 1973).

[42] Similarity of the marks is a hallmark of consumer confusion. See E. Remy Martin & Co., S.A. v. Shaw-Ross Int'l Imports, Inc., 756 F.2d 1525, 1531, 225 USPQ 1131, 1135 (11th Cir.1985) ("In evaluating the similarity of marks, we must consider ... the appearance, sound and meaning of the marks, as well as the manner in which they are displayed."). In this instance, however, the marks do not present a similar sound, meaning, or commercial impression. The MAGNIVISION mark is a single word; the MAGNA DOT mark consists of two words separated by a darkened circle. The MAGNIVISION mark has four syllables; the MAGNA DOT mark has three. The MAGNIVISION mark displays eleven letters, the last seven of which do not appear in the MAGNA. DOT mark; the MAGNA DOT mark has eight letters and a dot.

The only similarity between the marks is the MAGNA/MAGNI prefix. The record shows, however, that the MAGNA/MAGNI prefix as well as the VISION suffix enjoy wide use in the eyeglass industry on similar goods and services. This evidence included a number of registered trademarks for magnification lenses and eyeglasses MAGNA MAGNA ADD, MAGNA-BAR, MAGNA-COM, MAGNA-LITE, MAGNA-RULE, MAGNA-PAGE, MAGNATEL, MAGNA-SIGHTER, MAGNI-LENS, MAGNI-FOCUSER, MAGNI-STAT, MAGNI-SPECS, MAGNI-VIEWER, COOPERVISION, **VALLEN** VISION, ACURAVISION, CLEAR VISION, COOP VISION, COYOTE VISION, CRYSTAL VISION, POWER VISION, SELECT-A-VISION, TRUVISION, ULTRAVISION). The common usage of these descriptive terms weighs strongly against a finding of likelihood of confusion. See, e.g., Sun Banks of Fla., Inc., v. Sun Fed. Sav. & Loan Ass'n, 651 F.2d 311, 316, 211 USPQ 844, 849 (5th Cir.1981) ("[W]e find the extensive third-party use of the word 'Sun' impressive evidence that there would be no likelihood of confusion between Sun Banks and Sun Federal.").

The record shows that these trademarks appeared side-by-side on similar products and in similar retail outlets over a period of several years. Magnivision's own documents allege MAGNIVISION "has become the generic term for [over-the-counter] reading glasses ." Also. advertising Magnivision made extensive expenditures to promote the recognition of its mark. Nonetheless, the record contains *1331 no showing of actual confusion between the two marks.

The differences in the marks, the absence of actual confusion despite several years of simultaneous use in an identical market, the absence of evidence that VSI intended to copy Magnivision's mark, and the weakness of the descriptive MAGNIVISON mark add up to a finding of noninfringement as a matter of law. Accordingly, this court holds that no reasonable juror could have found infringement of the MAGNIVISION trademark by the MAGNA· DOT mark.

Unfair Competition

[43] [44] Because the only evidence of unfair competition in this case was Magnivision's claims of trademark and trade dress infringement, the jury's finding of unfair competition lacks substantial Unfair competition provides evidence. additional degree of protection above that provided by trademark and trade dress law. See Freedom Sav. & Loan Ass'n v. Way, 757 F.2d 1176, 1186, 226 USPQ 123, 130 (11th Cir.1985). Although trademark and trade dress infringement may be the basis for a claim of unfair competition, it frequently requires the court to examine additional conduct

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that would not give rise to a claim of trademark infringement. See id.

In this case, the only evidence in support of the unfair competition claims was the trademark and trade dress infringement claims. As stated earlier, no reasonable juror could find a likelihood of confusion between the trade dress and trademarks of VSI and Magnivision. Therefore, on the evidence presented, no reasonable juror could find that VSI engaged in unfair competition with Magnivision.

Personal Liability of Myron Orlinsky

[45] Title 35 authorizes a finding that an officer of a corporation is personally liable for the corporation's acts of infringement. See 35 U.S.C. § 271(a) (1994); Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 552, 16 USPQ2d 1587, 1593 (Fed.Cir.1990). Personal liability under § 271(a), however, requires sufficient evidence to justify piercing the corporate veil. See id. The corporate entity deserves respect and legal recognition unless specific, unusual circumstances justify disregarding the corporate structure. See id. The most common reason for disregarding the corporate structure is that the "corporation was merely the alter ego of its officers." Id.

[46] The record shows that Myron Orlinsky made the sole decision to continue using the hanger tags after VSI received cease and desist letters from Magnivision. The record, however, shows no further evidence of personal activity by Mr. Orlinsky. This evidence does not establish that Mr. Orlinsky overstepped his authority as CEO of VSI. Rather the record shows that Mr. Orlinsky acted consistent with his authority as CEO. Therefore, the record only supports the conclusion that Mr. Orlinsky acted within and according to the strictures of the corporate structure. The record shows no instance of the corporation operating as Mr. Orlinsky's alter ego. Thus, the record contains no evidence to justify piercing the corporate veil. See, e.g., id. at 553 ("Although these facts support the conclusion that the officers had knowledge of their acts, these acts were within the scope of their

employment and thus were protected by the corporate veil.")

Furthermore, after VSI received the cease and desist letter. Mr. Orlinsky consulted counsel before continuing to produce the Version 1 and 2 hanger tags. The record thus shows that Mr. Orlinsky acted pursuant to a good faith belief of noninfringement engendered by advice of counsel. Once again, this evidence does not justify rejecting legal recognition of the corporate structure. See id. at 553. In sum, the record does not contain sufficient evidence that Mr. Orlinsky acted outside of the scope of his employment or that he continued to manufacture the hanger *1332 tags knowing that they infringed Magnivision's patents.

IV.

In conclusion, although the district court erred in its construction of the claims of the '345, '726 and '911 patents, these errors were harmless because of the jury's finding of infringement under the doctrine of equivalents. This court therefore affirms the district court's decision not to grant judgment as a matter of law of non-infringement. The jury's findings with respect to trademark and trade dress infringement, however, are unsupported substantial evidence. Furthermore, because the finding of unfair competition rested solely on the findings of trademark and trade dress infringement, that finding is also unsupported by substantial evidence. The district court therefore erred in failing to grant judgment as a matter of law that VSI did not infringe Magnivision's asserted trademark and trade dress and that it did not engage in unfair competition. This court therefore reverses the decision of the district court not to grant judgment as a matter of law with respect to the absence of trademark and trade dress infringement and the absence of unfair competition. Additionally, because the jury findings of trademark and trade dress infringement and unfair competition lacked substantial evidence, the district court's entry of a permanent injunction was an abuse of discretion. The district court's entry of the permanent injunction is thus vacated to the extent it prohibited VSI from using its accused trademark, display cards

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and hanger tag color coding scheme. Furthermore, there is insufficient evidence to support holding Mr. Orlinsky personally liable for the damage award. The district court's conclusion to the contrary is therefore reversed.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART and REVERSED-IN-PART.

C.A.Fed. (Fla.), 1999. Al-Site Corp. v. VSI Intern., Inc. 174 F.3d 1308, 50 U.S.P.Q.2d 1161

Briefs and Other Related Documents (Back to top)

- 1999 WL 33645062 (Appellate Brief) Brief by Appellants Al-Site Corporation and Magnivision, Inc. in Opposition to Combined Petition for Panel Rehearing and for Rehearing En Banc (May. 13, 1999) Original Image of this Document (PDF)
- 1999 WL 33955269 (Appellate Petition, Motion and Filing) Combined Petition for Panel Rehearing and for Rehearing En Banc by Defendants-Cross Appellants VSI International Inc. and Myron Orlinsky (Apr. 13, 1999) Original Image of this Document with Appendix (PDF)
- 1998 WL 34097788 (Appellate Brief) Reply Brief of Defendants-Cross Appellants VSI International Inc. and Myron Orlinsky (Apr. 15, 1998) Original Image of this Document (PDF)
- 1998 WL 34097790 (Appellate Brief) Reply and Opposition Brief of Appellants Al-Site Corporation and Magnivision, Inc. (Mar. 06, 1998) Original Image of this Document (PDF)
- 1998 WL 34097792 (Appellate Brief) Brief of Defendants-Cross-Appellants VSI International Inc. and Myron Orlinsky (Jan. 20, 1998) Original Image of this Document (PDF)
- 1997 WL 33544957 (Appellate Brief) Brief for Appellants Al-Site Corporation and Magnivision, Inc. (Dec. 10, 1997) Original Image of this Document with Appendix (PDF)

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United States Court of Appeals, Federal Circuit. In re Brian W. BAIRD, Art F. Diaz, William H. Dickstein and Charles M. Seymour. No. 93-1262.

Jan. 19, 1994.

Examiner's final rejection of claims of patent application, entitled "Flash Fusible Toner Resins," as unpatentable on ground of obviousness was affirmed by the Board of Patent Appeals and Interferences. Applicants appealed. The Court of Appeals, Lourie, Circuit Judge, held that: (1) fact that many diphenols specifically enumerated in prior reference were derivatives of bisphenol A did not establish that reference suggested selection of bisphenol A itself in preparation of flash fusible toner, and (2) given vast numbers of diphenols encompassed by generic diphenol formula in reference, and fact that diphenols that reference specifically disclosed to be typical, preferred, and optimum were different from and more complex than bisphenol A, reference did not teach or fairly suggest selection of bisphenol A in preparation of flash fusible toner.

Reversed.

West Headnotes

[1] Patents 291 \$\iiist\$ 324.5

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.5 k. Scope and Extent of
Review in General. Most Cited Cases

Patents 291 324.55(2)

291 Patents

291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.55 Questions of Fact,
Verdicts, and Findings
291k324.55(2) k. Clearly Erroneous
Findings. Most Cited Cases
Federal Circuit Court of Appeals reviews
obviousness determination by Board of Patent
Appeals and Interferences de novo, while it reviews
underlying factual findings for clear error.

[2] Patents 291 \$\iins16.25\$

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases

Prior reference did not provide requisite motivation for selection of bisphenol A in preparation of flash fusible toner comprising polyester of bisphenol A and aliphatic dicarboxylic acid, and thus, reference did not teach or fairly suggest selection of bisphenol A in preparation of toner resin so as to render claim 1 of patent application unpatentable on ground of obviousness, even though generic diphenol formula of reference encompassed bisphenol A and reference specifically disclosed three dicarboxylic acids recited in claim, given vast number of diphenols encompassed by generic diphenol formula in reference and fact that diphenols that reference specifically disclosed to be typical, preferred, and optimum were different from and more complex than bisphenol A. 35 U.S.C.A. § 103.

[3] Patents 291 \$\iiist\$ 314(5)

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k314 Hearing
291k314(5) k. Questions of Law or
Fact. Most Cited Cases

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What reference teaches is question of fact.

[4] Patents 291 \$\infty\$16.25

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.25 k. Chemical Compounds. Most Cited Cases

Fact that claimed compound may be encompassed by disclosed generic formula does not by itself render compound obvious and unpatentable. 35 U.S.C.A. § 103.

[5] Patents 291 \$\infty\$16.25

291 Patents

291∏ Patentability

291II(A) Invention; Obviousness

291k16.25 k. Chemical Compounds. Most

Cited Cases

Fact that many of the diphenols specifically enumerated in prior reference were derivatives of bisphenol A of which flash fusible toner of claim 1 for which applicant sought patent was comprised did not establish that reference suggested selection of bisphenol A itself in preparation of toner so as to render claim unpatentable on ground of obviousness, where, according to specification, diphenol in esters of claim could only be bisphenol A, and not bisphenol A derivative. 35 U.S.C.A. § 103.

[6] Patents 291 \$\infty\$16.25

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.25 k. Chemical Compounds. Most

Cited Cases

Disclosure of millions of compounds does not render obvious and unpatentable claim to three compounds, particularly when that disclosure indicates preference leading away from claimed compounds. 35 U.S.C.A. § 103.

Patents 291 €=328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,634,649. Cited as a reference.

*380 John A. Brady, Lexmark Intern., Inc., Lexington, Kentucky, argued, for appellant. Adriene B. Lepiane, Asst. Sol., Office of the Sol., Arlington, VA, argued, for appellee. With her on the brief were Fred E. McKelvey, Sol. and Richard E. Schafer, Associate Sol.

Before MICHEL, PLAGER and LOURIE, Circuit Judges.

*381 LOURIE, Circuit Judge.

Applicants Brian W. Baird, Art F. Diaz, William H. Dickstein, and Charles M. Seymour (collectively Baird) FN1 appeal from the October 15, 1992 decision of the U.S. Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences, Appeal No. 92-0860, affirming the examiner's final rejection of claims 1-5 of application Serial No. 07/333,524, entitled "Flash Fusible Toner Resins," as unpatentable on the ground of obviousness under 35 U.S.C. § 103 (1988). We reverse.

FN1. The real party in interest is Lexmark International, Inc.

BACKGROUND

Baird's application is directed to a flash fusible toner comprising a polyester of bisphenol A and an aliphatic dicarboxylic acid. Synthesis of the toner compositions involves the acetylation of bisphenol A and the reaction of that product with an aliphatic dicarboxylic acid selected from the group consisting of succinic acid, glutaric acid, and adipic acid. The application discloses that toners containing bisphenol A have optimal characteristics for flash fusing including, *inter alia*, high thermal stability and low critical surface energy.

Claim 1, the only claim at issue, reads as follows:

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1. A flash fusible toner comprising a binder resin which is a bisphenol A polyester containing an aliphatic di[carboxylic] acid selected from the group consisting of succinic acid, glutaric acid and adipic acid.

Claim 1 stands rejected as obvious over U.S. Patent 4,634,649 to Knapp et al., which relates to developer compositions comprised of, *inter alia*, the polymeric esterification product of a dicarboxylic acid and a diphenol of the following generic formula:

$$H(OR)_{n_1O}$$
 R
 X'
 $Q(R"O)_{n_2H}$

wherein R is selected from substituted and unsubstituted alkylene radicals having from about 2 to about 12 carbon atoms, alkylidene radicals having from 1 to 12 carbon atoms and cycloalkylidene radicals having from 3 to 12 carbons atoms; R and R are selected from substituted and unsubstituted alkylene radicals having from 2 to 12 carbon atoms, alkylene arylene radicals having from 8 to 12 carbon atoms and arylene radicals; X and X are selected from hydrogen or an alkyl radical having from 1 to 4 carbon atoms; and each n is a number from 0 (zero) to 4.

Col. 4, lines 16-38. The Knapp formula contains a broad range of variables and thus encompasses a large number of different diphenols, one of which is bisphenol A, which is shown in Baird's application as having the following structure:

Knapp also discloses that the dicarboxylic acids have the general formula:

HOOCR n3COOH

*382 wherein R is a substituted or unsubstituted alkylene radical having from 1 to 12 carbon atoms, arylene radicals or alkylene arylene radicals having from 10 to 12 carbon atoms and n3 is a number of less than 2.

Col. 5, lines 6-14. Twenty typical dicarboxylic acids are recited, including succinic acid, glutaric acid, and adipic acid, the dicarboxylic acids recited

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in claim 1.

The examiner rejected claim 1 as obvious on the ground that Knapp specifically ciscloses as components of his esters the three dicarboxylic acids recited in claim 1 and a generic fermula which encompasses bisphenol A. Recognizing that bisphenol A is defined when certain specific variables are chosen, the examiner reasoned that bisphenol A "may be easily derived from the generic formula of the diphenol in [Knapp] and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the instant claim[] is to follow [that formula]."

The Board upheld the examiner's rejection. It rejected Baird's argument that there was no motivation for one to select bisphenol A from Knapp and summarily concluded that 'the fact that [the claimed] binder resin is clearly encompassed by the generic disclosure of Knapp ... provides ample motivation for the selection of [the claimed composition]." Slip op. at 3. The Board's decision was affirmed on reconsideration.

DISCUSSION

[1] The only issue before us is whether the record supports the Board's conclusion that, in view of the teachings of Knapp, the claimed compounds FN2 would have been obvious to one of ordinary skill in the art. We review an obviousness cetermination by the Board *de novo*, while we review underlying factual findings for clear error. *In re Beattie*, 974 F.2d 1309, 1311, 24 USPQ2d 1040, 1041 (Fed.Cir.1992).

FN2. Since the toner, the resin, and the polyester compounds appear to be treated in the Board opinion and patent application as synonymous, and the PTO has premised its obviousness rejection on the obviousness of the compounds, we will treat this case accordingly.

[2] Baird does not dispute the fact that the generic diphenol formula of Knapp encompasses bisphenol

A. Nor does Baird dispute that Knapp specifically discloses the three dicarboxylic acids recited in claim 1. Rather, Baird argues that there is no suggestion in Knapp to select bisphenol A from the vast number of diphenols covered by the generic formula and that the Board thus erred in concluding that the claimed compounds would have been obvious.

[3] [4] What a reference teaches is a question of fact. Beattie, 974 F.2d at 1311, 24 USPQ2d at 1041 . The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed.Cir.1992) (rejecting Commissioner's argument that "regardless [] how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it"). Jones involved an obviousness rejection of a claim to a specific compound, the 2-(2 -aminoethoxy)ethanol salt of 2-methoxy-3,6-dichlorobenzoic acid (dicamba), as obvious in view of, inter alia, a prior art reference disclosing a genus which admittedly encompassed the claimed salt. We reversed the Board's rejection, reasoning that the prior art reference encompassed a "potentially infinite genus" of salts of dicamba and listed several such salts, but that it did not disclose or suggest the claimed salt. Id.

In the instant case, the generic diphenol formula disclosed in Knapp contains a large number of variables, and we estimate that it encompasses more than 100 million different diphenols, only one of which is bisphenol A. While the Knapp formula unquestionably encompasses bisphenol A when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables. Indeed, Knapp appears to teach away from the selection of bisphenol A by focusing on more complex diphenols, including 2,2-bis(4-beta-hydroxyethoxyphenyl)propane, 2,2-bis(4-hydroxypropoxyphenyl)propane, and 2,2-bis(4-hydroxyisopropoxyphenyl)propane. Col. 4, lines 51-64. Knapp teaches that in preferred diphenols, R *383 has 2 to 4 carbon atoms and R and R have 3 to 4 carbon atoms, and in "optimum" diphenols, R is an isopropylidene radical, R and R

are selected from the group consisting of propylene

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and butylene radicals, and n is one. Col. 4, lines 38-47. Knapp further states that the diphenol in the preferred polyester material is 2,2-bis(4-hydroxyisopropoxyphenyl)propane. Col. 5, lines 36-38. Fifteen typical diphenols are recited. None of them, or any of the other preferred phenols recited above, is or suggests bisphenol A.

[5] The Commissioner repeatedly emphasizes that many of the diphenols specifically erumerated in Knapp are derivatives of bisphenol A. He argues that Knapp thus suggests the selection of bisphenol A itself. We disagree, because, according to the specification, the diphenol in the esters of claim 1 can only be bisphenol A, not a bisphenol A derivative. While Knapp may suggest certain complex bisphenol A derivatives, it does not describe or suggest bisphenol A and therefore does not motivate the selection of bisphenol A.

[6] "[A] reference must be considered not only for what it expressly teaches, but also for what it fairly suggests." In re Burckel, 592 F.2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979). Given the vast number of diphenols encompassed by the generic diphenol formula in Knapp, and the fact that the diphenols that Knapp specifically discloses to be " typical," "preferred," and "optimum" are different from and more complex than bisphenol A, we conclude that Knapp does not teach or fairly suggest the selection of bisphenol A. See In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed.Cir.1993) (DNA sequence would not have been obvious in view of prior art reference suggesting a nearly infinite number of possibilities and failing to suggest why among all those possibilities one would seek the claimed sequence). A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.

CONCLUSION

The Board clearly erred in finding that Knapp would have provided the requisite motivation for the selection of bisphenol A in the preparation of

the claimed compounds. Accordingly, the decision of the Board affirming the rejection of claim 1 as obvious over Knapp is reversed.

COSTS

No costs.

REVERSED

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59 C.C.P.A. 1256, 465 F.2d 896, 175 U.S.P.O. 169 (Cite as: 59 C.C.P.A. 1256, 465 F.2d 896)

P

United States Court of Customs and Patent Appeals. Application of Arthur W. LANGER, Jr. and Raymond R. Haynes. Patent Appeal No. 8731.

Sept. 14, 1972.

Proceeding in matter of application for a patent. The Board of Patent Appeals of the United States Patent Office, Serial No. 467,109, affirmed decision of the primary examiner finally rejecting as unpatentable specified process claims, and applicant appealed. The United States Court of Customs and Patent Appeals, Lane, J., held that claimed invention consisting of process of copolymerizing an alpha-olefin and a sterically hindered alkenyl amine in the presence of a Ziegler-type catalyst was not rendered unpatentable, as obvious in view of prior art, by presence in reference patent of an isolated hindered amine falling outside scope of applicant's claims.

Reversed.

West Headnotes

[1] Patents 291 \$\infty\$16(2)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16 Invention and Obviousness in

General

291k16(2) k. Prior Art in General.

Most Cited Cases

(Formerly 291k18)

In determining whether a claimed invention is unpatentable as obvious in view of the prior art, the prior art as a whole must be compared with the claimed subject matter as a whole. 35 U.S.C.A. § [2] Patents 291 \$\infty\$16.25

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.25 k. Chemical Compounds. Most

Cited Cases

(Formerly 291k18)

While prior art disclosure of homologues of compounds may be found to render prima facie obvious claims to those compounds, homology should not be automatically equated with prima facie obviousness. 35 U.S.C.A. § 103.

[3] Patents 291 \$\infty\$16.4

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.4 k. Results and Means of

Producing. Most Cited Cases

(Formerly 291k18)

Claimed invention consisting of process of copolymerizing an alpha-olefin and a sterically hindered alkenyl amine in the presence of a Ziegler-type catalyst was not rendered unpatentable, as obvious in view of prior art, by presence in reference patent of an isolated hindered amine falling outside scope of applicant's claims. 35 U.S.C.A. § 103.

Patents 291 328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original. Most Cited Cases

3,293,326. Cited as prior art.

**896 *1257 David A. Roth, Houston, Tex., atty. of record, for appellant. M. F. Fincke, S. W. Brock, Jr., John S. Schneider and Thomas B. McCulloch,

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Houston, Tex., of counsel.

S. Wm. Cochran, Washington, D. C., for the Commissioner of Patent. Fred W. Sherling, Washington, D. C., of counsel.

Before RICH, Acting Chief Judge, ALMOND, BALDWIN, and LANE, Judges, and CLARK, Justice, United States Supreme Court, sitting by designation.

LANE, Judge.

This is an appeal from that portion of the decision of the Board of Appeals sustaining the examiner in rejecting process claims 11 and 14-17 FN1 of appellants' application FN2 as unpatentable under 35 U.S.C. § 103 for obviousness over a patent to Jezl et al. (Jezl). FN3 Our review of the record and arguments in this case convinces us that the board erred, and we accordingly reverse.

> FN1. On appeal to the board, the application included product claims in addition to these process claims, and the board affirmed the examiner's rejection of the product claims as well. However, appellants have expressly withdrawn the product claims from this appeal.

> FN2. Serial No. 467,109 filed June 25, 1965.

FN3. U. S. Patent No. 3,293,326 issued December 20, 1966, on an application filed July 6, 1965, as a continuation-in-part application of one filed June 17, 1960.

claimed invention is a process of copolymerizing an alpha-olefin and a sterically hindered alkenyl amine in the presence of a Ziegler-type catalyst. In the specification, appellants explain that prior to their invention the polymerization of alpha-olefins, such as ethylene and propylene, to form, for example, **897 polyethylene and polypropylene, was well known, as was the copolymerization of monomers, such as ethylene and propylene, to polyethylene-polypropylene copolymers. Both types of polymerization were known to be performed in

presence of Ziegler-type, or organometal-transition metal, catalyst. It appears that it was also known that the introduction of amine sites into a poly (alpha-olefin) would lend dyeability to the polymer since such sites are receptive to available dye compounds. Appellants therefore sought an alpha-olefin-amine copolymer. A problem in realizing this objective is said to have been that Ziegler-type catalysts are deactivated by polar compounds, such as amines, with which they react. Appellants' solution to the problem was the selection of alkenyl amines which are sterically hindered at the amine site, i.e., *1258 which have a structure and spatial arrangement of the component atoms such that reaction is retarded or inhibited.

Claim 11 is the broadest claim on appeal and reads as follows:

11. A copolymerization process which comprises contacting under polymerization conditions in the presence of an organo-metal-transition metal catalyst and [sic] alpha-olefin containing 2 to 10 carbon atoms and an alkenyl amine having one of the following formulae:

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59 C.C.P.A. 1256, 465 F.2d 896, 175 U.S.P.Q. 169 (Cite as: 59 C.C.P.A. 1256, 465 F.2d 896)

where: R1 is an alkenyl radical containing 4 to 12 carbon atoms;

R2 and R3 are selected from the group consisting of hydrogen and an alkyl group containing 1 to 8 carbon atoms, with the sum of carbon atoms of R2 and R3 being less than 13;

R4 is an alkyl group containing 1 to 4 carbon atoms; R5 is selected from the group consisting of hydrogen and an alkyl group containing 1 to 4 carbon atoms:

R6 is an alkenyl radical containing 2 to 12 carbon atoms; and of the groups R 1, R2 and R3, at least two of the groups have a carbon branch at the alpha or beta positions from the nitrogen atom; and R5 may be hydrogen provided the group R1 has a carbon branch at the alpha or beta position from the nitrogen atom.

Dependent claims 14-17 recite specific process conditions, materials, and proportions of materials. The limitations on the process imposed in these claims are not relevant to the issues on appeal.

The sole reference relied upon is the Jezl patent. Like appellants, Jezl was concerned with imparting dyeability to poly (alpha-olefins) and discloses accomplishing this by copolymerizing alphaolefins with alkenyl amines in the presence of a Ziegler-type catalyst. Jezl discloses**898 using terminally unsaturated alkenyl amines and recites a long list of suitable amines. We need not review the many amines disclosed by Jezl for the Board and the solicitor relied on only one, N,

N-di-2-ethylhexyl-4-pentenylamine. This concededly a sterically hindered *1259 amine of the type contemplated by appellants, although it does not fall within the scope of the definition of suitable amines recited in the appealed claims. Appellants assert that the named amine is the only amine disclosed by Jezl which is structurally similar to those found by appellants to be suitable for use with Ziegler-type catalysts, all the other Jezl amines being unhindered. Nothing said by the board in either its original opinion or its opinion pursuant to appellants' request for reconsideration, and nothing argued by the solicitor, is inconsistent with that assertion. The solicitor's case is built entirely on the named amine. We therefore approach this case from the premise that Jezl names one sterically hindered amine for use in the same process as appellants and many other amines, all of which are unhindered.

The board held as follows:

Jezl discloses the use of, *inter alia*, a[n] N, N-di-2 ethylhexyl-4-pentenyl amine which falls outside the artificial formula of * * * [claim] 11 by having 2 alkyl radicals with a total of 16 carbon atoms instead of the upper limit of 13 set forth in the formula. This illustrative compound is described as producing copolymers with alpha olefins and there is nothing to suggest that it does not do this as effectively as do the homologous unsaturated amines of appellants' claim 5 [which defined the amine as N, N-diisopropyl-3-butenylamine and which was in the group of product claims withdrawn from appeal].

Indeed, it might be expected that the illustrative amine serves more effectively its process and

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product purpose than many of the amines called for in appellants' claims * * * 11, and 14 to 17 because it is a polymeriz-Jezl et al. specify that their amine able terminally unsaturated amine. monomer must terminally and unsaturated appellants specifically identify no useful amine having anything other than terminal unsaturation in its alkenyl group.

Appellants' principal argument with respect to Jezl et al. appears to be that the patent does not show the same "structure" as that claimed, by which we assume that appellants refer to their limitation on the total number of alkyl carbon atoms in the amine. This number is not shown to be "critical," or to distinguish the effective, from the ineffective compounds.

The solicitor asserts that this case should be resolved on the basis of homology of the named amine in Jezl and appellants' amines which compels, in his view, a holding of prima facie obviousness which stands unrebutted.

Appellants urge that Jezl shows no appreciation for the problem solved by them and that as a result, there is no basis for selecting the one amine relied upon and finding the use of sterically hindered amines to have been obvious to one of ordinary skill in the art.

OPINION

[1] [2] We find ourselves in agreement with appellants' position in this case. As elementary as it may be to patent law under the 1952 Act, the concept of having to show obviousness of the invention "as a whole," *1260 as required by 35 U.S.C. § 103, is especially appropriate to bear in mind in this appeal. See In re Aufhauser, 399 F.2d 275, 55 CCPA 1477 (1968); In re Hoeksema, 399 F.2d 269, 55 CCPA 1493 (1968). That concept supersedes "rules" which might emerge from the repeated application of other principles which may ordinarily be correct but fail under a set of facts which bring such principles in conflict with the broader notions of § 103. **899 So it is that while this court has found the prior art disclosure of

homologues of compounds to render prima facie obvious claims to those compounds, see, e.g., In re Ackermann, 444 F.2d 1172, 58 CCPA 1405 (1971); In re Papesch, 315 F.2d 381, 50 CCPA 1084 (1963) , homology should not be automatically equated with prima facie obviousness. The facts of the present case strain to the breaking point such an equation.

[3] We view appellants' invention "as a whole" as being the use of sterically hindered amines as opposed to unhindered amines in a known process to solve a particular problem. We find no challenge to appellants' contentions that the problem of catalyst deactivation exists and the use of sterically hindered amines as a class solves it. We do not think the Jezl patent provides a basis for the use of sterically hindered amines as a class, or of any of the amines encompassed by appellants' claims, in the Jezl process. The presence in the reference of an isolated hindered amine falling outside the scope of appellants' claims does not, by itself, apprise the ordinary artisan of the significance of hindered amines as a class. Compare In re Kuderna, 426 F.2d 385, 389, 57 CCPA 1078, 1083-1084 (1970).

This court has said that "[a]ll of the disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art." In re Boe, 355 F.2d 961, 965, 53 CCPA 1079, 1083 (1966). Under the facts in Boe, that concept brought non-preferred embodiments within the purview of prior art subject matter against which the claimed subject matter could be compared. However, the concept cuts both ways, and when "all of the disclosures in a reference" are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference. Compare In re Sebek, Cust. & Pat.App., 465 F.2d 904, decided August 31, 1972. In effect, we compare the prior art "as a whole" with the claimed subject matter "as a whole." Doing so in the present case convinces us of the error in the board's decision, and we accordingly reverse.

Reversed.

Cust. & Pat.App., 1972

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Application of Langer 59 C.C.P.A. 1256, 465 F.2d 896, 175 U.S.P.Q. 169

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Westlaw.

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(Cite as: 958 F.2d 347)

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United States Court of Appeals, Federal Circuit. In re Rita S. JONES, Michael T. Chirchirillo and Johnny L. Burns.

No. 91-1380.

Feb. 28, 1992.

The Patent and Trademark Office, Board of Patent Appeals, rejected claim of patent and appeal was taken. The Court of Appeals, Rich, Circuit Judge, held that salt of acid commonly known as "dicamba" was not obvious.

Reversed.

West Headnotes

[1] Patents 216.25

291k16.25 Most Cited Cases

Patent and Trademark Office failed to present prima facie case of obviousness with respect to patent claim for novel salt of acid commonly referred to as "dicamba," used as herbicide; claimed salt was primary amine with ether linkage, structurally different from diethanolamino salt disclosed by closet prior act, which was secondary amine without ether linkage, and there was no evidence that one of ordinary skill in herbicidal art would have been motivated to make modifications of prior art salt needed to arrive at claimed salt. 35 U.S.C.A. § 103.

[2] Patents = 16.25

291k16.25 Most Cited Cases

Disclosure of chemical genus does not render obvious any species that happens to fall within it.

[3] Patents 2114.16

291k114.16 Most Cited Cases

(Formerly 291k114.15)

Before Patent and Trademark Office may combine disclosures of two or more prior art references in order to establish prima facie obviousness, there

must be some suggestion for doing so, found either in references themselves or in knowledge generally available to one of ordinary skill in art. 35 U.S.C.A. § 103.

*348 Melvyn M. Kassenoff, Sandoz Corp. Patent & Trademark Dept., East Hanover, N.J., argued for appellant; Gerald D. Sharkin and Richard E. Vila, East Hanover, N.J. and Joanne M. Giesser, Palo Alto, Cal., on brief.

Harris A. Pitlock, Associate Sol., Arlington, Va., argued for appellee; Fred E. McKelvey, Sol., on brief (Richard E. Schafer, Patent & Trademark Office, of counsel).

Before RICH, ARCHER, and CLEVENGER, Circuit Judges.

RICH, Circuit Judge.

Rita S. Jones et al. (collectively Jones) appeal from the April 15, 1991 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), Appeal No. 90-1920, sustaining the rejection of claim 1, the only claim of application Ser. No. 07/099,279, titled "The 2-(2'-Aminoethoxy)-Ethanol Salt of Dicamba," as unpatentable under 35 U.S.C. § 103. We conclude that the PTO has not presented a prima facie case of obviousness, and therefore reverse.

The Invention

The claimed invention is a novel salt of 2-methoxy-3,6-dichlorobenzoic acid, which acid is commonly referred to as "dicamba." A known herbicide, dicamba has typically been sold in the form of its known dimethylamine salt.

The sole claim of the application on appeal reads:

1. The 2-(2'-aminoethoxy) ethanol salt of dicamba. The claimed salt has the following structure:

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*349 The Rejection

Claim 1 stands rejected as obvious in view of the combined teachings of the following references:

Richter	U.S. Patent No. 3,013,054	Dec. 12, 1961
Moyle et al.	U.S. Patent No. 3,056,669	Oct. 2, 1962
Balassa	U.S. Patent No. 3,725,031	Apr. 3, 1973
Zorayan et al.	88 Chem. Abstracts No. 52300j	1978
Wideman	86 Chem. Abstracts No. 43711a	1977

Richter, which all agree is the closest prior art, discloses dicamba in free acid, ester, and salt forms, for use as a herbicide. Among the salt forms disclosed are substituted ammonium salts, a genus which admittedly encompasses the claimed salt. Richter does not specifically disclose the claimed 2-(2'- aminoethoxy) ethanol salt, however. Most notably, Richter discloses (emphasis and bracketed word ours):

Compositions in which X is substituted ammonium are amine salts 2-methoxy-3,6-dichlorobenzoic acid [dicamba] and are prepared by the addition of the free acid to various amines. Typical amines which can be used to prepare such amine salts are dimethylamine, trimethylamine, triethylamine, diethanolamine, triethanolamine, isopropylamine, morpholine, and the like. The resulting products respectively, the dimethylamino, trimethylamino, triethylamino, diethanolamino, triethanolamino, isopropylamino, and morpholino salts 2methoxy-3,6-dichlorobenzoic acid.

Zorayan teaches the amine $(H_2N(CH_2CH_2O)_2H)$ used to make the claimed salt, as well as the use of that amine in the preparation of surfactants for shampoos, bath preparations, and emulsifiers.

Wideman also teaches the amine disclosed in Zorayan.

The content of the remaining references is unnecessary to our decision.

The Board upheld the examiner's rejection of claim as obvious, finding that the claimed 2-(2'-aminoethoxy) ethanol salt of dicamba and the diethanolamine salt of dicamba specifically disclosed by Richter were "closely related in structure," and that based upon the expectation that "compounds similar in structure will have similar properties," a prima facie case of obviousness had arisen. The Board found that Jones' rebuttal evidence (Rule 132 declarations and data reported in the specification) failed to "compare the claimed subject matter with the closest prior art," and accordingly did not serve to rebut the prima facie

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case. This appeal followed.

Analysis

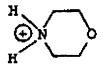
[1][2] The Solicitor contends that the claimed salt falls within the genus of substituted amine salts of dicamba disclosed by Richter, and that, like Richter's genus, the claimed compound has herbicidal activity. Thus, the Solicitor urges, under the circumstances of this case, (1) the genus/species relationship and (2) the common utility of the claimed and prior art compounds support the Board's holding of prima facie obviousness. Moreover, the Solicitor adds, although the claimed compound is neither a homolog nor a position isomer of those salts specifically disclosed in Richter, it is structurally similar thereto, particularly the diethanolamino salt noted by the Board.

The question of "structural similarity" in chemical patent cases has generated a body of patent law unto itself. [FN1] Particular types *350 or categories of structural similarity without more have, in past cases, given rise to prima facie obviousness; see, e.g., In re Dillon, 919 F.2d 688, 692-94, 16 USPO2d 1897, 1900-02 (Fed.Cir.1990) (tri-orthoesters and tetra-orthoesters), cert. denied, 500 U.S. 904, 111 S.Ct. 1682, 114 L.Ed.2d 77 (1991); In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers); In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologs and structural isomers); In re Hoch, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). However, none of these types of structural similarity are involved here. And in any event, this court has previously stated that generalization is to be avoided insofar as specific structures are alleged to be prima facie obvious one from the other. In re Grabiak, 769 F.2d 729, 731, 226 USPQ 870, 872 (Fed.Cir.1985).

> FN1. See generally Helmuth A. Wegner, "Prima Facie Obviousness of Chemical Compounds," 6 Am.Pat.L.Assoc.Q.J. 271 (1978).

On the basis of the record before us, we cannot sustain the Board's conclusion that the claimed salt and the diethanolamino salt disclosed by Richter are so "closely related in structure" as to render the former prima facie obvious in view of the latter. The claimed salt is a primary amine with an ether linkage. The diethanolamino salt disclosed by Richter is a secondary amine, without an ether linkage:

In addition, the only substituted ammonium salt of dicamba expressly disclosed by Richter having an ether linkage is the morpholino salt, which is cyclic in structure:



The claimed salt is, plainly, acyclic; i.e., linear. Lastly, while the isopropylamino salt disclosed by Richter is a primary amine, as is the claimed salt, its iso-structure is quite different:

The lack of close similarity of structure is not negated by the fact that the claimed salt is a member of Richter's broadly disclosed genus of substituted ammonium salts of dicamba. The Solicitor contends that "[t]he relative size of the genus disclosed by the prior art would not appear to be a controlling factor in determining whether a prima facie case of obviousness exists for a species encompassed within the described genus," citing Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 806-09, 10 USPQ2d 1843, 1845-48 (Fed.Cir.), cert. denied, 493 U.S. 975, 110 S.Ct. 498, 107 L.Ed.2d 502 (1989). We decline to extract from Merck the rule that the Solicitor appears to suggest--that

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regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it. In Merck, at issue on appeal was whether claims to a composition of two diuretics, amiloride and hydrochlorothiazide, present in a particular "medically synergistic" weight ratio, would have been obvious in view of a specific prior art disclosure of amiloride in combination with hydrochlorothiazide. one of combinations disclosed in the prior art reference. Id. at 806, 10 USPQ2d at 1845. Based on the facts before it, including evidence at trial that the experimentation needed to arrive at the claimed dosage was "nothing more than routine," id. at 809, 10 USPQ2d at 1847, the court held that the claimed invention would have been obvious. In contrast, though Richter discloses the potentially infinite genus of "substituted ammonium salts" of dicamba, and lists several such salts, the salt claimed here is not specifically disclosed. Nor, as we have explained above, is the claimed salt sufficiently similar in structure to those specifically disclosed in Richter as to render it prima facie obvious. Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts.

[3] *351 The Solicitor points out that, given the breadth of forms of dicamba (free acid, ester, or salt) disclosed by Richter as having herbicidal utility, one of ordinary skill in the art would appreciate that the dicamba group has significance with respect to imparting herbicidal activity to dicamba compounds. Thus, the Solicitor contends, one skilled in the art would have been motivated to use, with dicamba, substituted ammonium salts made from a known amine, such as the amine disclosed by Zorayan and Wideman, and would have expected such a salt to have herbicidal activity. Before the PTO may combine the disclosures of two or more prior art references in order to establish prima facie obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed.Cir.1988). We see no such suggestion in Zorayan, which is directed to shampoo additives, nor in Wideman, which teaches that the amine used to make the claimed compound is a byproduct of the production of morpholine. Nor does the broad disclosure of Richter fill the gap, for the reasons discussed above.

Conspicuously missing from this record is any evidence, other than the PTO's speculation (if it be called evidence) that one of ordinary skill in the herbicidal art would have been motivated to make the modifications of the prior art salts necessary to arrive at the claimed 2-(2'-aminoethoxy) ethanol salt. See Grabiak, 769 F.2d at 731-32, 226 USPQ at 872 ("[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/ [claimed] thioester change in structure, in order to complete the PTO's prima facie case and shift the burden of going forward to the applicant."); In re Lalu, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed.Cir.1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.")

Conclusion

We conclude that the PTO did not establish a prima facie case of obviousness, and thus did not shift to Jones the burden of coming forward with unexpected results or other objective evidence of non-obviousness. Accordingly, the decision of the Board is

REVERSED.

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(Cite as: 121 U.S.P.Q. 345)

C

Ex parte BURTNER AND BROWN

Patent Office Board of Appeals

Patent issued Aug. 19, 1952

Opinion dated Nov. 26, 1951

United States Patents Quarterly Headnotes

PATENTS

[1] Patentability--Composition of matter (§ 51.30)

Prior art esters differ from claimed esters by CHsub2 or multiple of CHsub2, but critical question is not whether alcohol moieties of esters are homologous, but whether alcohols are sufficiently similar from standpoint of structural chemistry so that those now claimed would be suggested to chemists from those disclosed and would be expected to have like properties.

PATENTS

Particular patents-Alkyl Esters

2,607,777, Burtner and Brown, N-Alkyl Piperidyl Alkyl Esters of Diphenyl Acetic Acid and 9-Fluorenyl Carboxylic Acid, claims 12 to 16 of application allowed; rejection of claims 17 to 20 reversed.

*345 Appeal from Division 6.

Application for patent of Robert R. Burtner and John M. Brown, Serial No. 740,712, filed Apr. 10, 1947. From decision *346 rejecting claims 12 to 20, applicants appeal. Reversed.

SMITH, OLSEN & BAIRD and WARREN D. MCPHEE, both of Chicago, Ill., for applicants.

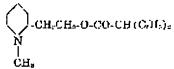
Before RICHARD, GENIESSE, and DUNCOMBE, Examiners in Chief.

GENIESSE, Examiner in Chief.

This is an appeal from the action of the examiner finally rejecting claims 12 to 20, inclusive, all of the claims in the case.

Claim 15 is reproduced as illustrative:

15. An acid addition salt of a basic ester of the formula



wherein the nitrogen-containing ring is completely saturated.

Appellants list the following references as relied on by the examiner:

Miescher, 2,079,962, May 11, 1937.

Miescher, 2,143,491, Jan. 10, 1939.

Wolfes, 2,221,828, Nov. 19, 1940.

Walter, 2,229,533, Jan. 21, 1941.

Rieveschl, 2,377,040, May 29, 1945.

Burtner, 2,387,879, Oct. 30, 1945.

Burtner and Cusic, "Journal of the American Chemical Society," 1943, pages 262-267.

The examiner in addition lists the following references as ancillary art:

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Saudborn et al., Chemical Abstracts--Vol. 22 (1928) p. 963.

Marvel et al., Chemical Abstracts--Vol. 23 (1929) p. 1902

Winterfield et al., Chemical Abstracts--Vol. 29 (1935) p. 7331

Rabe et al., Chemical Abstracts--Vol. 32 (1938) p. 8420-1

Renshaw et al., Chemical Abstracts--Vol. 33 (1939) p. 3379-80

Tullock et al., Chemical Abstracts--Vol. 33 (1939) p. 4250

Prelog et al., Chemical Abstracts--Vol. 33 (1939) p. 7797

Prelog et al., Chemical Abstracts--Vol. 38 (1944) p. 6289

The appealed claims relate to somewhat complex esters, that of claim 15, reproduced above, representing the elected species.

The claims refer to the acid addition salts as well as the basic esters. Since it is conventional to prepare acid addition salts of complex amino compounds, the distinction between the acid addition salt and the basic ester is not of significance and we will discuss the ester itself rather than the addition salt thereof.

The acid moiety of the ester of claim 15 is diphenylacetic acid. Claims 13, 14 and 16 also relate to esters of this acid. Claims 17, 18, 19 and 20 relate to esters of 9-fluorene carboxylic acid. Claim 12 is generic to esters of both of the above mentioned acids. The alcohol moiety of the ester of claim 15 is a derivative of piperidine having a methyl group at the 1 (that is at nitrogen) position and an ethanol radical at the 2 position. The remaining claims define the alcohol moiety of the ester in broader language but all of these claims require a lower alkyl radical on the nitrogen and an

alkanol radical on one of the carbons of the piperidine ring. The piperidine ring is a six-membered saturated ring containing 5 carbons and 1 nitrogen in the ring. The ancillary references cited by the examiner show that the alcohol moiety of the presently claimed esters is old and that such alcohols have heretofore been esterified with acids other than the acids defined in the claims on appeal. Since this is conceded by appellants we need not further consider these ancillary references.

Claims 12 to 16 have been rejected as unpatentable over the prior art, the Miescher et al., and Burtner patents being considered the most pertinent. These references show esters of diphenylacetic acid and of 9-fluorene carboxylic acid. The alcohol moiety of the reference esters are said by the examiner to be members of the same homologous series as are the alcohol moieties of the claims on appeal. The empirical formula of certain of these alcohols of the prior art differ from those of the claims on appeal by multiples of CH sub2 and the examiner was of the opinion that such alcohols belong to the same general class and have similar properties and are accordingly homologous. He therefore insists that there must be some evidence that the presently claimed esters possess beneficial properties not possesed by the esters of the prior art. See In re Henze, 37 CCPA 1009, 1950 C.D. 319, 85 USPQ 261. Appellants on the other hand vigorously challenge the examiner's holding that the compounds of the references are sufficiently similar to those here claimed to justify placing such esters (or the alcohol moieties thereof) in the same homologous series.

The Miescher et al. patent 2,079,962 discloses an ester of diphenylacetic acid with 2-piperidinoethanol. In this compound the alkanol radical is attached to the nitrogen atom of the piperidine ring and there is no independent alkyl radical *347 on the nitrogen. The Miescher et al. patent 2,143,491 discloses the diphenylacetic acid ester of tropine. The tropine is a bi-cyclic compound in which one of the two fused rings may be considered a piperdine ring. There is a methyl group on the nitrogen but the alcohol, that is, the hydroxy group is attached to the ring carbons

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directly rather than through an alkylene radical as required by the claims on appeal.

The Burtner patent describes an ester of 9-fluorene carboxylic acid with an N-alkyl piperidine. The alcohol moiety of this ester differs from that claimed in that the hydroxyl group is directly attached to a ring carbon rather than through an alkylene radical. The patentee, Burtner, is one of the joint applicants in the present case. Burtner refers to diphenylacetic acid esters as well as esters of the fluorene acid.

[1] It will be evident from the standpoint of empirical formula, the esters of the first mentioned Miescher patent as well as that of Burtner differ from those herein claimed by CH sub2 or a multiple of CH sub2. The alcohols of these three references differ in the relative positions of the functional or reactive groups, that is, the amino nitrogen and the hydroxyl. We are of the opinion that the critical question is not whether or not the alcohol moieties of the esters under consideration are to be considered "homologus" under some of the available definitions of that term, but whether or not the alcohols are sufficiently similar from the standpoint of structural chemistry so that those now claimed would be suggested to chemists from those disclosed and would be expected to have like properties. See the Henze decision cited above as well as In re Jones, 32 CCPA 1020, 1945 C.D. 304, 65 USPQ 480. The last mentioned decision recognized distinctions between compounds of the benzene and naphthalene series as sufficient to justify the allowance of the claims on appeal. The court in passing also recognized differences between compounds wherein a hydroxy group was attached to a benzene nucleus and one in which the hydroxy compound was attached to a benzene nucleus through an alkylene linkage.

The question in issue is not free from difficulty. It will be apparent that while the class of compounds here claimed possesses a considerable degree of complexity, the art has been active in at least closely related fields. We are of the opinion that

under the circumstances of the present record that the rejection should not be sustained. The claimed compounds differ in at least two respects from the nearest reference, that is, Miescher and Burtner.

The rejection of claims 12 to 16, inclusive, as unpatentable over the art will not be sustained.

Claims 17 to 20, inclusive, were refused solely on the ground that they were not inclusive of the elected species. The rejection was proper when made and appellants do not challenge the holding on which it is based, but in view of the allowance of generic claims, these claims will be subject to further consideration by the examiner.

The decision of the examiner is reversed.

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Application No.: 10/700,417 Appeal Brief

RELATED PROCEEDINGS APPENDIX

Application No.: 10/700,417 Appeal Brief

RELATED PROCEEDINGS APPENDIX

None